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APPENDIX B
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U.S. DEPARTMENT OF DEFENSE

SMALL BUSINESS INNOVATION RESEARCH PROGRAM
PHASE 1 — FY 1987
PROJECT SUMMARY

Topic No. A87-284 Military Department/Agency US ARMY

Name and Address of Proposing Small Business Firm

MICROWAVE MEDICAL SYSTEMS, INC. (MMS)
52 SOUTH AVENUE, BLDG #7, M/S-704
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Name and Title of Principal Investigator

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Proposal Title

IN-LINE MICROWAVE WARMER FOR BLOOD AND INTRAVENOUS FLUIDS

Technical Abstract (Limit your abstract to 200 words with no classified or proprietary information/data.)

To address the problem of hypothermia and its associated coagulopathy and cardiac dysfunction occuring with trauma, a technique has been conceived that provides in-line heating of blood and intravenous(IV) fluids. The design is based on a microwave generator and chamber capable of uniform heating of fluids during the infusion process. An in-line unit overcomes the delay inherent with remote warming and the cooling occurring in a cold environment during transport of fluid or blood heated at a remote location.

During the Phase I study a heating chamber with a wound bobbin of IV tubing has been developed that predictably and uniformly distributes a microwave energy field along the entire fluid path within the chamber. To determine the efficacy of the rapid, in-line warming of blood and IV fluids within this uniform microwave energy field, *in-vitro* tests(primarily with blood) have been conducted. Results confirm the rapidity and uniformity of the predicted heat transfer mechanism; laboratory analysis of the *in-vitro* blood samples warmed by the system show no significant changes in constituency from the control samples.

To address the need for a feedback control mechanism to vary the delivered level of microwave energy as a function of flow rate and input temperatures, radiometric transducers have been designed, fabricated and evaluated for non-invasive temperature measurement of the flowing fluid. Results show that the response times of a microwave radiometry system using these transducers at the inlet and outlet ports of the heating chamber and within the heating chamber itself are sufficient for reliable feedback control.

Anticipated Benefits/Potential Commercial Applications of the Research or Development

The technique developed in the Phase I program has the potential of being developed into a device suitable for field use in quickly heating(in-line) blood or intravenous fluids administered in the pre-hospital treatment of hypothermia. The design can be developed into a unit that is small in size and suitable for field use.

Also possible with this system is non-invasive, passive temperature monitoring of fluids flowing through IV tubing. The combination of uniform heating and in-line temperature monitoring allows for the configuration of a feedback mechanism capable of maintaining constant temperature of fluids with varying flow rates.

List a maximum of 8 Key Words that describe the Project.

Trauma, Fluid Warming, Blood Warming, Hypothermia, Microwave

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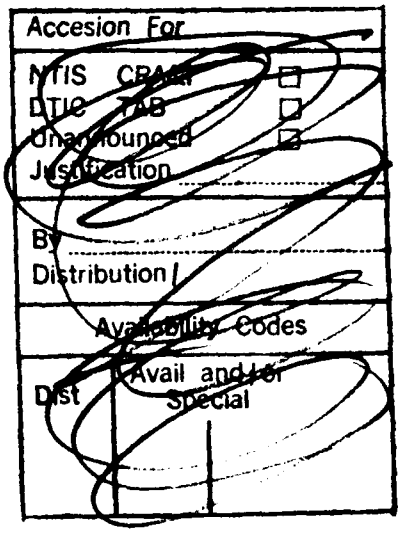


1.0 INTRODUCTION

1.1 Background

A general requirement exists to provide improved field care after traumatic injury when evacuation is delayed as described by Topic A87-284 in the DOD SBIR program solicitation of 9 January 1987. This topic asks for state-of-the-art applications designed to stabilize pathophysiological processes after traumatic injury.

Hypovolemic shock, secondary to traumatic exsanguination, is the most common cause of death in severely injured sodiers as identified by the Broad Agency Announcement guide for the U.S. ARMY Medical Research and Development Command of August, 1986[1]. Treatment of hypovolemic shock is the subject of the Phase I study proposed here by Microwave Medical Systems, Inc(MMS).

Three important factors for successful treatment of hypovolemic shock include the administration of different types of fluids, rapidity of infusion of these fluids and prevention of hypothermia[2-5]. To address the problem of hypothermia and its associated coagulopathy occuring with trauma, Microwave Medical Systems Inc(MMS) has designed a device capable of in-line heating of intravenous(IV) fluids.

The design incorporates microwave energy for heating and passive, non-invasive microwave radiometry to monitor fluid temperature as shown in **Figure 1**. The work completed in the Phase I study demonstrates the efficacy of the system and the feasibility of configuring the system into a small, portable unit that will provide controlled warming without invading the normal infusion pathway. The follow-on Phase II program is intended to optimize the system for military and commercial applications.

1.1.1 Battlefield Applications

The treatment of traumatic injuries occuring in the battlefield often requires restoring normothermia and infusion of fluids, such as saline or blood, into the patient. These two treatments are inter-related since the transfusion of cold fluids can further aggravate the hypothermic condition of the patient as shown by Boyan et. al[2]. Adverse effects on body physiology from hypothermia have been identified by many investigators including the USA Cold Regions Test Center in a report on "Arctic Personnel Effects"[6] and include the following:

- Decrease in heart rate, blood pressure, cardiac output and coronary blood flow[7-10].
- Reduction in tissue oxygenation. As body temperature drops, the affinity of oxygen for the hemoglobin molecule increases. This mechanism, in turn, impairs the transfer of oxygen from the hemoglobin molecule to the tissue[7,11].
- Heart failure in the form of ventricular fibrillation or ischemia. These conditions can result from myocardial cooling induced by the infusion of cold fluids into the central venous system[7-9].
- Loss of effectiveness of coagulation[7,9,11,12].
- Depressed hepatic function[7,12].

A 1985 clinical study by Slotman et al, showed that hypothermia(at temperatures less than 97°F) intraoperatively is associated with increased mortality[13]. These investigators recommend agressive rewarming of hypothermic patients.

IV FLUID & BLOOD WARMER: *Block Diagram*

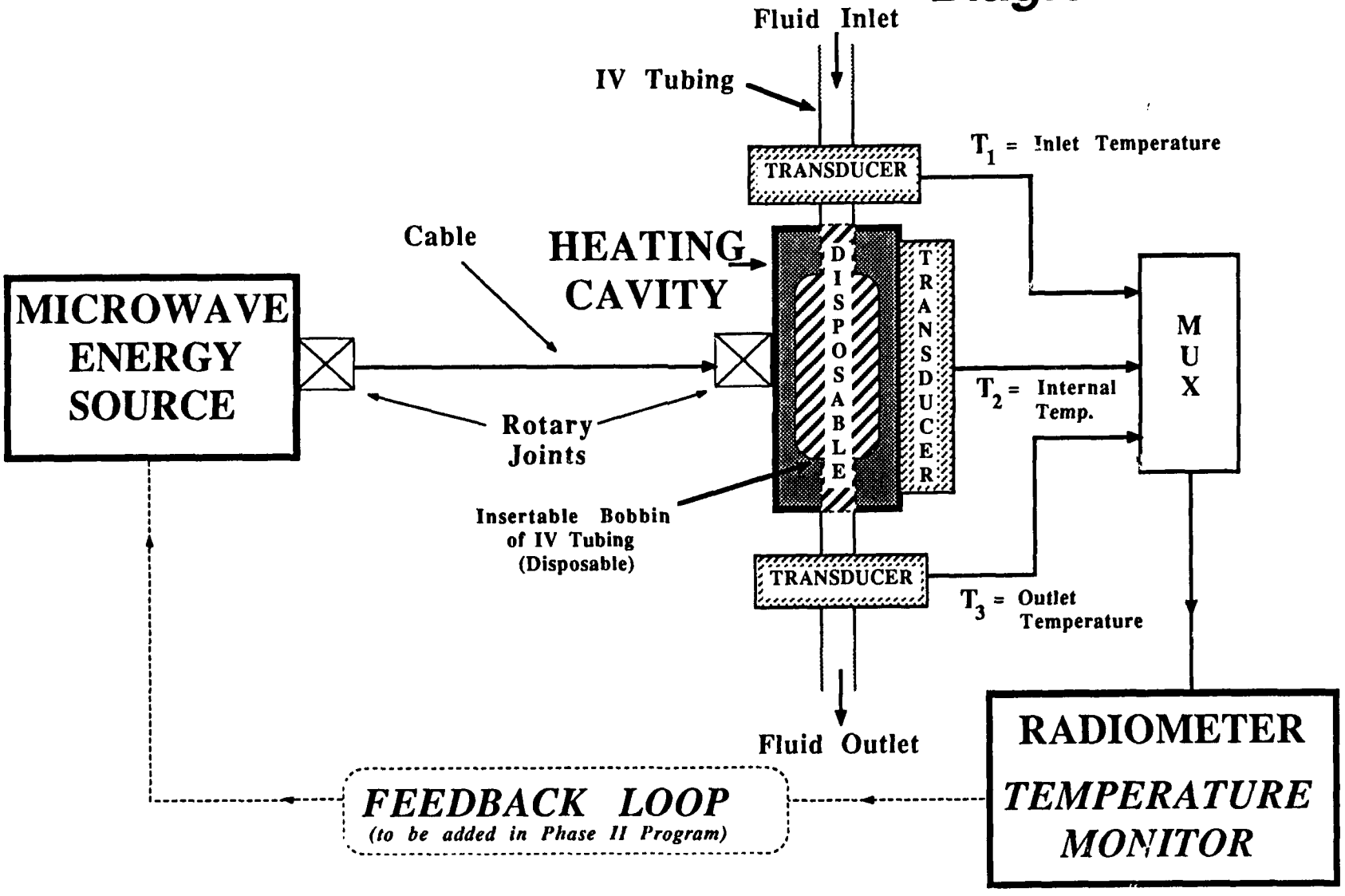


Figure 1. Block Diagram of Microwave Blood and IV Fluid Warmer with Radiometric Temperature Monitoring

The recognition of hypothermia as a serious threat to the patient has led to the introduction of standard techniques to combat this condition. But these techniques are limited to the emergency room or operating room because conventional equipment to treat hypothermia is not portable. For mild cases of hypothermia, patients are usually warmed passively by apparatus such as warming blankets or heated rooms. For severe cases of hypothermia or for conditions involving hemodynamic compromise, patients are actively warmed by methods that heat the core circulation[7] such as inhalation of warmed vapor, gastric and/or peritoneal lavage and warmed, centrally-administered IV fluids.

The Phase I study addresses the need for an in-line fluid warmer that could be used in the field for the treatment of traumatic injury and associated hypothermia. A small, portable fluid warmer unit that is an integral part of the infusion path may help reduce the high mortality rates associated with the pre-hospital support phase of trauma by bringing the fluid-warming capability in close proximity to the patient. An in-line unit overcomes the delay inherent with remote warming and the cooling occurring in a cold environment during transport of fluid heated at a remote location. Currently, in-line administration of warmed IV fluids to the patient is accomplished in the operating room by commercially available heat exchangers which incorporate long lengths of tubing submersed in a warm water bath for heat transfer. This heat exchange instrumentation is impractical for field or ambulance use because it requires a large circulating volume of heated water. In addition, the long path length of these heat exchangers presents increased problems of blood coagulation or clotting.

1.1.2 Civilian Applications

Hypothermia and and its associated coagulopathy occurring with trauma is the leading cause of death in young Americans. Trauma occurs from near drowning, accidents involving the thorax, puncture wounds and other mishaps. Today patients still die in operating rooms from uncontrollable hemorrhage secondary to hypothermic coagulopathy. The design proposed here for a small, portable in-line fluid warmer could be utilized as early as the pre-hospital phase of support where intravenous fluids are given.

Additional applications of in-line fluid warmers include warming blood in an extracorporeal circulation(ECC) path in the operating room and/or intensive care unit. Heating of blood in an ECC path is becoming more important and gaining widespread usage in at least two procedures:

1) **Extracorporeal Membrane Oxygenation(ECMO)**[14,15]
It is estimated that almost 75,000 persons each year will die of acute respiratory insufficiency caused by lung disease alone. ECMO addresses the problem of treating acute respiratory insufficiency by using external pumping and membrane oxygenation to assist the weakened or failing heart. Here, heat exchangers are necessary in the circulation path to prevent water loss through the membrane oxygenator associated with evaporative heat loss.

2) **Coronary Artery Bypass Grafting(CABG) Operations**[14,16,17]
This same in-line heating capability can be used during CABG procedures. Here, temperature elevation is required to restore normal body temperature in response to hypothermic cardioplegic arrest induced prior to the operation.

1.2 System Requirements

There are three major characteristics required for a system to warm blood and IV fluids in line for infusion into trauma victims:

RAPID

Rapidity of heating a cold fluid to normal body temperature is essential, since the well-being of trauma patients depends on the speed of treatment. Infusion rates can range from 100 ml/min up to 500 ml/min.

UNIFORM

"Hot-Spots" are often associated with rapid warming, particulary with warming of fluids using conventional microwave ovens. The design of a microwave warming device customized for warming IV fluids, in particular blood, can provide a heating pattern that is without "hot-spots".

In studies investigating treatment of hypothermia by infusion of warm fluids investigators have suggested "safe" minimum and maximum temperatures for these fluids. Several investigators, including Russell[18] and the Finnish Red Cross Blood Transfusion Service headed by Linko[19,20], estimate that 32°C would be the minimum acceptable temperature for a blood warmer to maintain body temperature within the "safe" range. Additionally, the Finnish group[20], found that heating above 46.8°C caused hemolysis. These critical temperatures are guidelines to be used in the design of in-line blood/IV fluid warmers.

CONTROLLED

In order to provide warm fluid to the patient at a constant temperature, the rate of warming must be controlled as a function of the flow rate and temperature of the cool fluid entering the system.

Here, the accuracy of maintaining a constant temperature of the fluid to be administered to the patient depends on the sensitivity and response time of the sensors(or transducers) detecting temperature at various points in the flow circuit and the ability to use the sensor information efficiently in a feedback control loop. An additional requirement is that in order to maintain the sterility of the IV circuit, the sensors must be non-invasive. A technique that satisfies all of these requirements is microwave radiometry, which has been used in the past by Microwave Medical Systems, Inc.(MMS) to measure thermal activity passively and non-invasively in biological tissues[24-28]. For this application, radiometric transducers can be incorporated into the feedback control loop to monitor temperatures at various points in the flow circuit.

In order to demonstrate and evaluate the performance of the microwave fluid warming system regarding the above three requirements, a test fixture(**Figure 2**) has been assembled and used in this Phase I study to measure the following:

- **Heating Capacity of Energy Source**
  Measurement of the temperature elevation of various fluids flowing through the system at specified flow rates.
- **Effectiveness of Radiometric Monitoring of Temperature**
  Sensitivity and response time of the radiometry system and transducers to detect the change in temperature of fluids flowing the circuit.
- **Efficacy of Blood Warming**
  Constituency of collected samples of blood warmed by the microwave heating device as compared to control(unheated) samples.

TEST FIXTURE

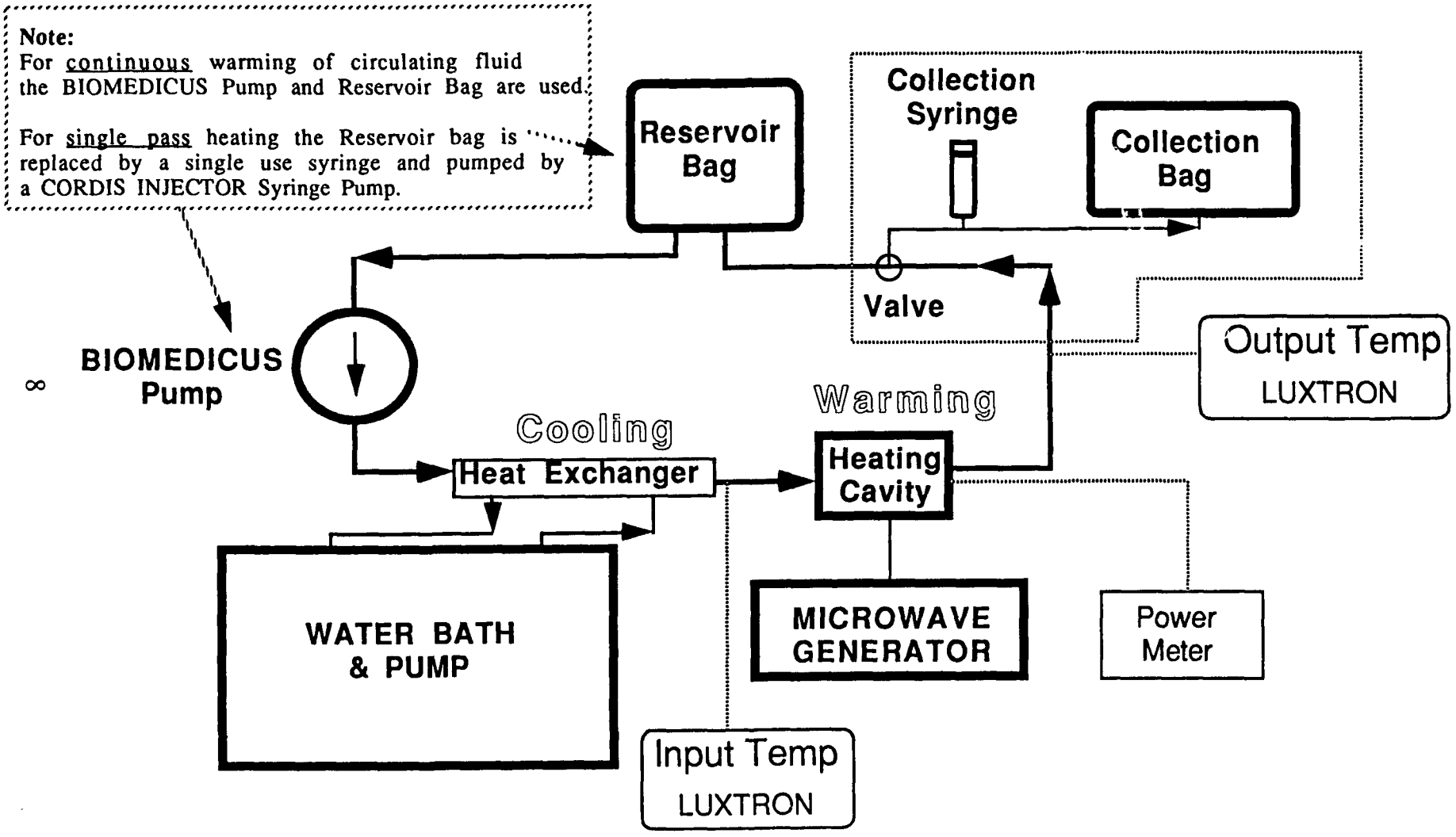


Figure 2. Test Fixture used to evaluate performance of Microwave Blood and IV Fluid Warmer

1.3 Summary of Salient Results

The Phase I feasibility study successfully demonstrated that the microwave heating and temperature monitoring technique is efficacious and efficient for rapid, uniform and controlled in-line warming of blood and IV fluids during the infusion process.

- **Sufficient Heating Capacity of System**
  A 400 watt energy source has been used to heat cool fluids from a temperature of 10°C to 37°C at flow rates of 200 ml/min. Heating capacity at other flow rates was measured and all results compared favorably with the expected *(calculated)* temperature rise.

- **Uniform Temperature Profile of Fluid Heating Path**
  The uniformity and efficiency of microwave absorption by the water-rich load of IV fluid or blood within the heating cavity can be determined by measuring the return loss and insertion loss of the cavity. Results show an insertion loss of 8 dB in the forward direction and a return loss of 28 dB. These results are very encouraging, since they indicate a 99.5% absorption of the incident microwave energy.

  To empirically determine the uniformity of heating, a small(1mm diameter) flexible fluoroptic probe was inserted into the heating path for temperature meaurement. No "hot-spots" were found, temperature elevation occured in a *steady progression upward from* the cool temperatures at the inlet port to the maximum temperature detected at the outlet port. Furthermore, a "worst-case" scenario of heating the fluid with a sufficiently high power and sufficiently slow flow rate to achieve a 60°C outlet temperature showed no "melting" or deformation of the PVC IV tubing. If there were "hot-spots" that caused local temperatures within the heating cavity to rise 5°C or 10°C above that seen at the outlet port then the PVC tubing would show deformation.

- **Effective Temperature Monitoring Capabilities**
  At the inlet and outlet ports of the heating cavity, the passive, non-invasive microwave radiometry technique can detect changes of 0.75°C with a response time of less than one second. More important is the capability of the technique to monitor temperatures within the cavity itself. This is important, in the event that flow completely stops and temperature changes at the outlet port are negligible. A transducer designed to measure temperatures of the fluid circuit that is inside the heating cavity has successfully been mounted within one wall of the heating cavity. The capability of this transducer to monitor the Average temperature of the fluid within the cavity was demonstrated.

- **Efficacy of Heating IV Fluids with the Microwave Warming Device**

  IV Fluids warmed by the system were examined to determine if any increase in plastisizer levels were caused by the in-line microwave heating through common PVC IV tubing. Only trace levels of the plasticisizer were detected when 0.9% Normal Saline and Ringer's Lactate were heated with the microwave device. These trace levels were also present in the control samples.

- **Efficacy of Heating Blood with the Microwave Warming Device**

  Blood samples were run through the system at various flow-rates. Samples were run through the system under four conditions:

  1) Control (Unheated): Run through the system once with power off
  2) One-Pass Heating: Run through the system once with power on
  3) Two-Pass Heating: Run through the system twice with power on
  4) Three-Pass Heating: Run through the system thrice with power on

  For one-pass heating, examination of the results of blood samples showed no significant differences in hematologic data were produced from that of the control(unheated) samples. The biochemical aspects also showed the absence of any statistically significant differences between the control and the one-pass samples.

  The only statistically significant difference found for two-pass and three-pass heating was in Lactic acid dehydrogenase(LDH), the absolute levels of which were clinically normal. Changes recorded here maybe attributable to increased handling of the samples or to heating effects alone, and not necessarily to any effects caused by microwave heating.

2.0 OBJECTIVES

The development program for in-line warming of blood and intravenous fluids uses microwave energy for heating and passive, non-invasive microwave radiometry to measure and monitor fluid temperature as shown in **Figure 1.**

The objectives of the Phase I Study as stated in the Phase I grant proposal are summarized as follows:

(1) Design a microwave warming device that takes advantage of the electromagnetic absorptive properties of water-rich media such as blood and intravenous(IV) Fluids:

- Design and fabricate a microwave energy source that can supply sufficient power for heating fluids from refrigeration temperatures up to normal body temperature at flow rates ranging from 100 ml/min to 500 ml/min.
- Design and fabricate a heating cavity that will be small and lightweight; and configured to create an area of uniform heating around a removable "insert" of IV tubing. The design of this "insert" will lead to the development of a sterile, disposable bobbin of IV tubing for the production version of the device.

(2) Fabricate a test fixture that demonstrates the practicality of the design and addresses problems inherent to a fluid warmer:

- Rapid, uniform heating of blood and IV Fluids
- Energy source that is non-invasive to the fluid path
- Sufficient energy available to heat fluids in-line at rates compatible with those commonly used in treating trauma patients
- Sufficient energy available to heat fluids from room temperature or refrigeration temperatures up to normal body temperature
- Small, portable size

(3) Investigate the effectiveness of measuring the temperature of the heated fluid with thermistor, thermocouple and radiometry systems

- Use a commercially available fluoroptic thermometry system to measure input/output temperatures by <u>invasive</u> placement of probes in the IV fluid path.
- Configure an existing 4.7 GHz microwave radiometer for temperature measurement of fluids in motion, <u>non-invasive</u> to the IV fluid path. Design tranducers for placement internal to the heating cavity and external at the cavity's input/output ports.

(4) Demonstrate the efficacy of warming blood with the device by statistical analysis of changes in the following parameters:

- Complete blood count (CBC): Hematocrit (Hct)
- Free Plasma hemoglobin(PlHgb)
- Serum haptoglobin (Hapto)
- Red cell Hematocrit
- Electrolytes: Potassium (K^+)
- Serum Enzymes: Lactic acid dehydrogenase (LDH)

and by cursory examination ofthe following parameters:

- White Cell Count
- Red Cell Volume
- Urea Nitrogen
- Total Protein
- Albumin
- Creatine Phosphokinease
- Alkaline Phosphotase

3.0 MATERIALS AND METHODS

3.1 Configuration of Phase I System

The three main subsystems of the blood and IV fluid warming system used in this Phase I study consists of the following:

1) **Microwave Energy Source**

- This generator produces microwave power at a frequency of 2450 MHz. A 400 watt source was adapted from a conventional microwave oven for use in this study. An interface circuit consisting of a waveguide-to-coaxial adapter was fabricated to connect the source to the heating cavity. Microwave energy produced by the source is channeled to the heating cavity where it is absorbed by the flowing, cool, water-rich fluids.

2) **Heating Cavity**

- The development of the heating cavity was the most significant accomplishment of the Phase I effort. The design of the heating cavity is essentially the same as that proposed by Microwave Medical Systems, Inc (MMS) in the original Phase I grant proposal. This design was proposed specifically for in-line warming of blood and fluids in the field or hospital emergency room where speed, small size and portability is essential. It is capable of delivering energy quickly(i.e., within seconds) but also uniformly(i.e., without "hot-spots) to cool fluids administered intravenously to trauma patients. The work for the Phase I study included fabrication of the heating cavity and tuning of the cavity to create an optimum design for efficient and uniform heat absorption by the fluid flowing through the cavity.

  The heating cavity consists of two parts: (1) the enclosure itself and (2) a labyrinth pathway of conventional IV tubing wound on a bobbin. Within this cavity the fluid is heated as it travels through the labyrinth by the energy supplied from the microwave generator. The plastic tubing carrying the fluids is transparent to microwave energy at this frequency. Bobbin design and orientation is optimized for most efficient absorption of the heating energy by the fluid flowing through the IV tubing.

3) **Temperature Monitor**

- Microwave radiometry techniques have been adapted for use in this system to monitor the temperature of the fluid flowing thoughout the system. These techniques have been previously developed by MMS for measuring subcutaneous thermal activity in biological tissue passively and noninvasively[24-28].

  Transducers, whose design was specified in the Phase I grant proposal, have been fabricated to interface non-invasively with IV tubing. These transducers are then connected to a microwave radiometer for measuring microwave emisivitty associated with thermal activity of fluids at three sites in the system:

  - Inlet Port of Heating Cavity
  - Internal Path of Heating Cavity
  - Outlet Port of Heating Cavity

3.2 Microwave Energy Source

The microwave energy source consists of two main components: 2450MHz Generator and a Heating Cavity. These two components are connected through an interface that channels the power from the Magnetron of the Generator through a Waveguide-to-Coaxial transition block to the heating cavity where the energy is absorbed by the cool IV fluid or blood.

3.2.1 Generator

The energy source, adapted from the Transformer and Magnetron of a commercially available microwave oven is shown in **Figure 3.**

The present energy source provides a constant power output of 400 watts. All heating of samples run through the system in this Phase I study was done using this source. In Phase II, the energy source will be configured to provide variable power to the heating cavity so that energy levels can be delivered that are proportional to the flow rates. The energy control mechanisms that exist on conventional commerically available microwave ovens pulse the filament voltage of the magnetron on and off to produce an average power over a given time interval of typically 30 seconds. This 30 second time interval is much too large to be used in the in-line blood/fluid warmer application where flow rates through the blood warmer can be as high as 8.3 ml per second(equivalent to 500 ml/min). For our application a continuous energy level or a pulsed energy source with a pulse repetition rate in the order of 20 to 50 msecs is desirable.

Preliminary work on the design of a solid-state controlled energy source with continuously variable energy levels has been done in this Phase I program and is shown in **Figure 4.** Further development work on this circuit will be part of the follow-on Phase II program. The mode of operation of this control circuit is to place a controlled switch in the circuit such that it opens and closes to allow current flow for a fraction of each cycle. This method of power control is commonly used for motor speed control and incadescent lamp dimmers. With this method the filament voltage is <u>not</u> turned off as with the power control mentioned above for conventional microwave ovens. The duration of the voltage applied to the filaments can be varied to achieve the desired level of average power over a 16.7 millisecond time base(note: duration of 60 Hz signals is 16.7 msecs). A preliminary design for such a control circuit is sketched in **Figure 4** ; this design will be developed as part of the follow-on Phase II effort.

In the circuit of **Figure 4**, the current conduction to the magnetron can be continuously controlled by varying the gate voltage of the Silicon Controlled Rectifier (SCR). An optocoupler is added to the circuit for electrical isolation between the control circuit and the high voltage SCR switching circuit.

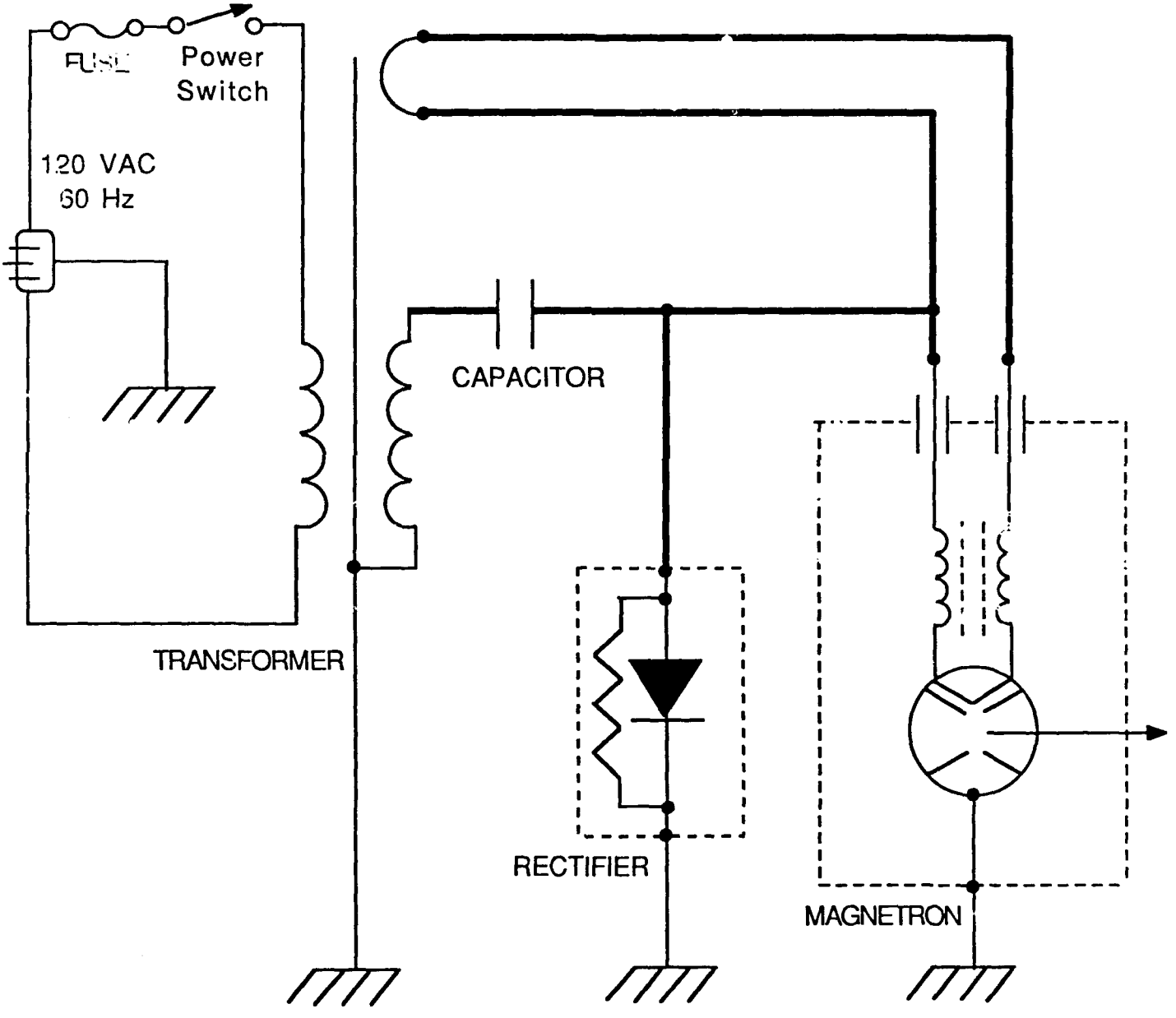


FIGURE 3. Microwave Energy Source
(Adapted from Power Source on Microwave Oven)

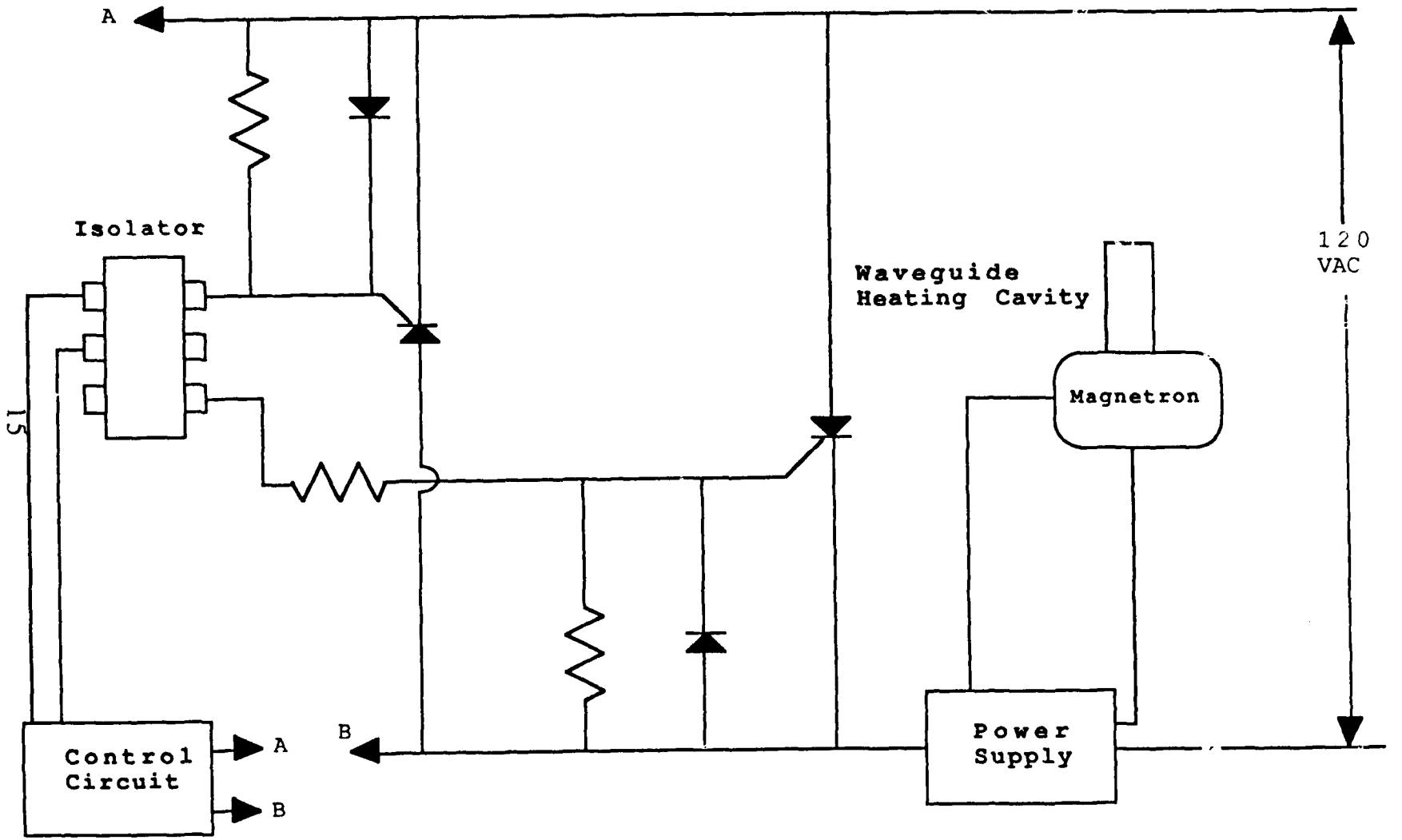


FIGURE 4. Proposed design for Solid State Control of Microwave Energy Source

3.2.2 Heating Cavity

Fabrication of two variations on the original cavity design, as specified in the original Phase I proposal, was completed. One design, shown in **Figure 5**, contains a slot in one of the the side walls to accept the radiometric transducer for monitoring the temperature of the fluid inside the cavity. A second configuration has the radiometric transducer placed in the front end wall. Both of these configurations were evaluated for their temperature monitoring capabilities and the results shown in **Section 4** show that both configurations are acceptable for monitoring temperature of the fluid flowing along the bobbin.

The heating cavity is designed to propagate power to the IV tubing bobbin assembly at a frequency of 2.45 GHz. The cavity is constructed in standard waveguide (WR430) with inside dimensions of length x width x height = 5.1" x 4.3" x 2.15". The radiometric transducer is in effect a waveguide detection antenna (WR187) operating at 4.7 GHz and built into one wall of the WR430 waveguide as shown in **Figure 5.**

The scope of work in the Phase I study did not include simultaneous operation of microwave heating and microwave temperature monitoring. However the effect of the presence of the temperature monitoring transducer on heating capacity was tested. Results tabulated in **Section 4.1** show that the microwave characteristics of the heating cavity with the bobbin full of liquid, as measured by the return loss, remain about the same with and without the transducer in place. The placement of the transducer on the Front-End Plate of the heating cavity thus has a negligible effect on the heating performance. The total power isolation between the Power Input probe of the heating cavity and the Radiometric Output probe of the transducer was measured to be approximately 80 dB.

Components inside the heating cavity are:

(1) **Bobbin** holding a length of IV Tubing wound in a spiral along the long axis of the bobbin. The original bobbin design specified in the Phase I proposal is shown in **Figures 6 and 8.** It is comprised of 1/8" O.D. IV tubing helically wound around the perimeter of a 1.2" diameter by 2" tall cylinder of Teflon. During the Phase I study the design has been optimized in shape and length of IV tubing wrapped around its longitudonal axis to give a uniform heating pattern. At present the length of tubing wrapped around the bobbin and inside the heating cavity is approximately 19 inches. This is a dramatic reduction from the original length of 78 inches. In the original configuration, the tubing length of 78 inches contained approximately 10 ml of fluid.

(2) **Connector/Tuning Elements:**

- **Power Input Connector with Launch** channels the microwave energy field from the source into the heating cavity.

- **Inductive Tuning Posts** provide fine tuning of the heating cavity to maximize the return loss of the heating cavity with a fluid filled bobbin to the desired frequency of 2.45 GHz. Since the efficiency of the heating cavity is directly related to the return loss, maximizing return loss is very important. These posts, in effect, allow the heating cavity to direct the energy field near and around the bobbin.

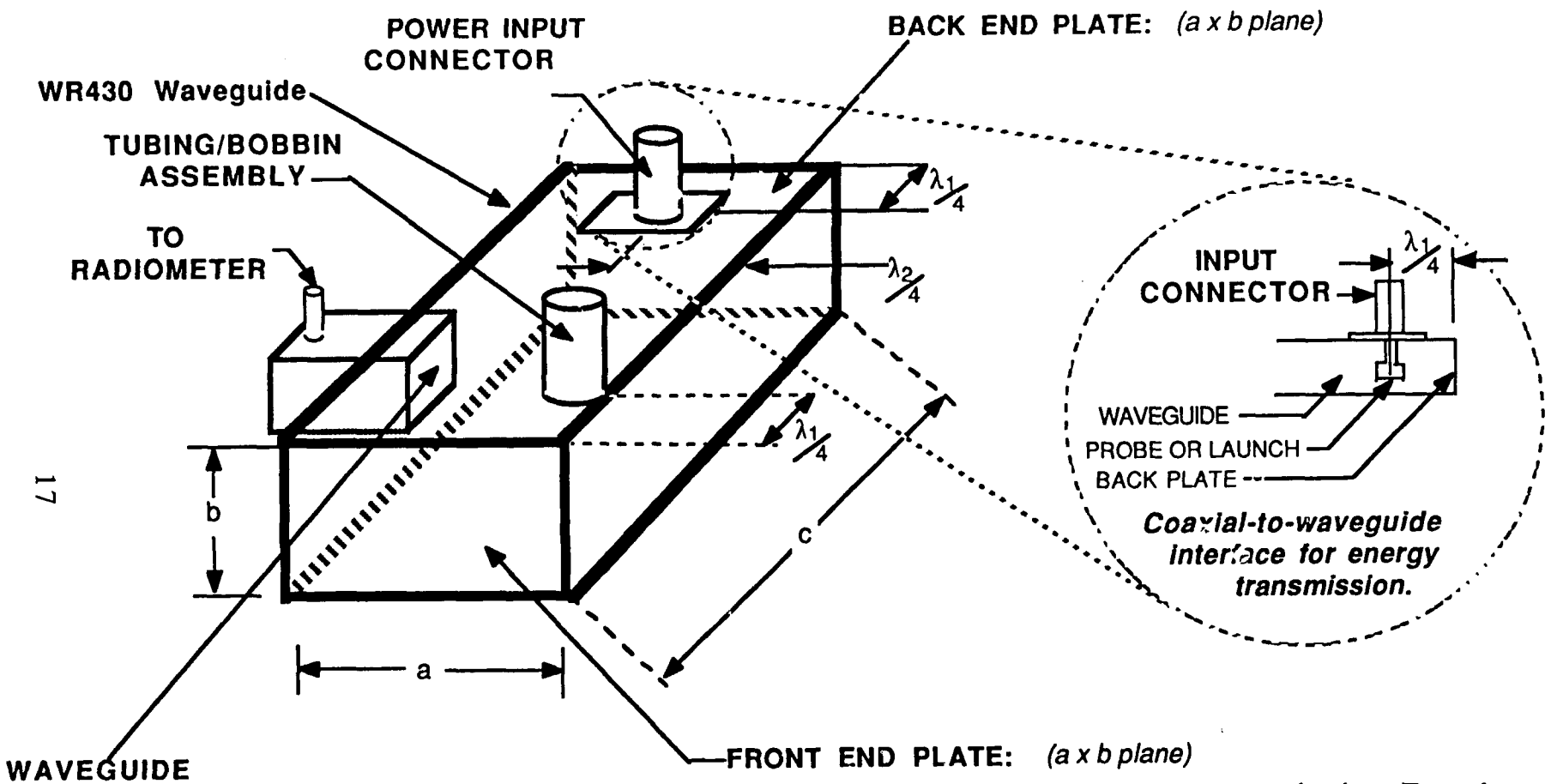


FIGURE 5. SKETCH OF HEATING CAVITY USED IN PHASE I
with bobbin insert & transducer for temperature monitoring

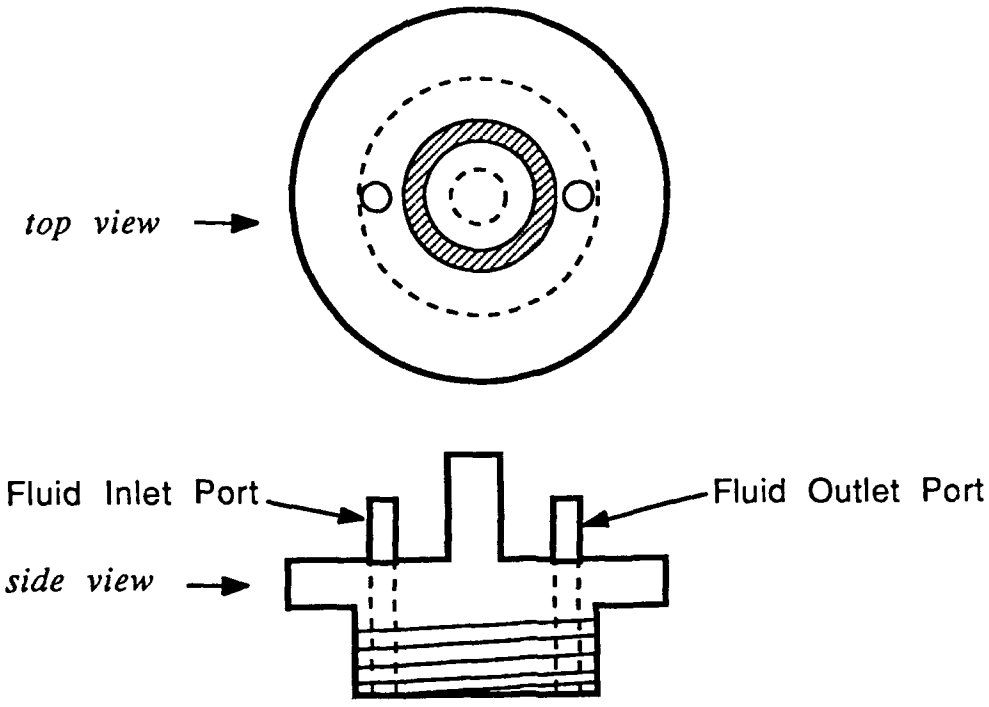


Figure 6a Sketch of Aluminum Cap for Bobbin.
Holes for inserting IV Tubing(Input & Output Ports).
Threads for screwing into heating cavity.

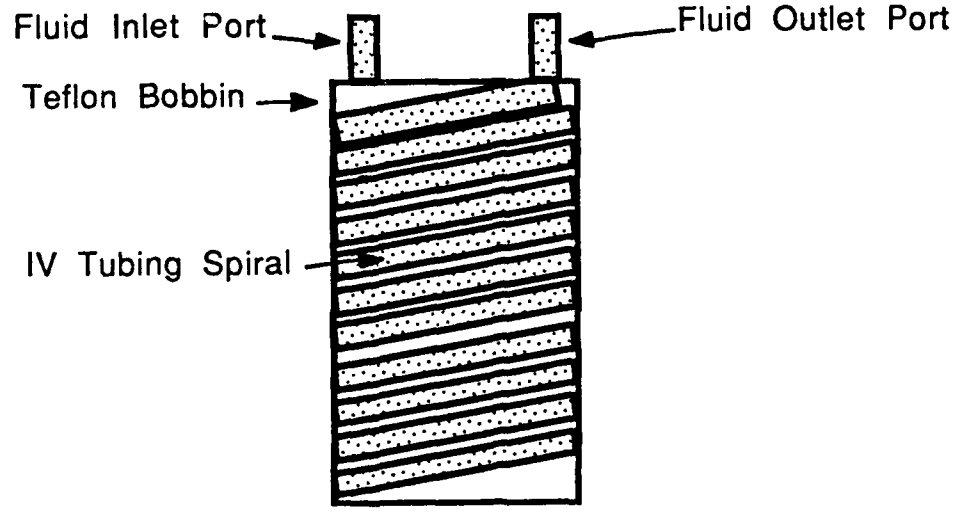


Figure 6b. Sketch of Teflon Bobbin with IV Tubing Spiral
(This bobbin was fabricated according to the original design specified in the Phase I proposal. Variations in tubing length and spiral dimensions were evaluated during the Phase I study.)

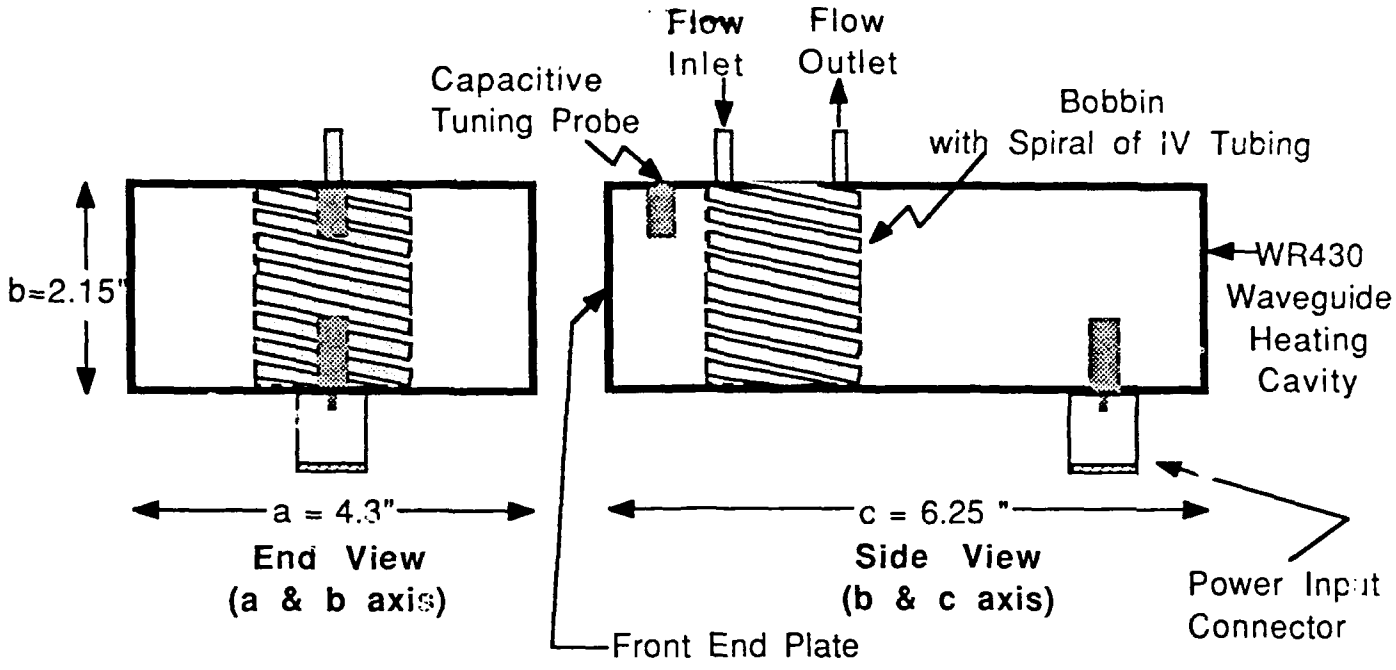


FIGURE 7a. HEATING CAVITY : Original Configuration (Bobbin#1) (78" IV tubing wound along b axis)

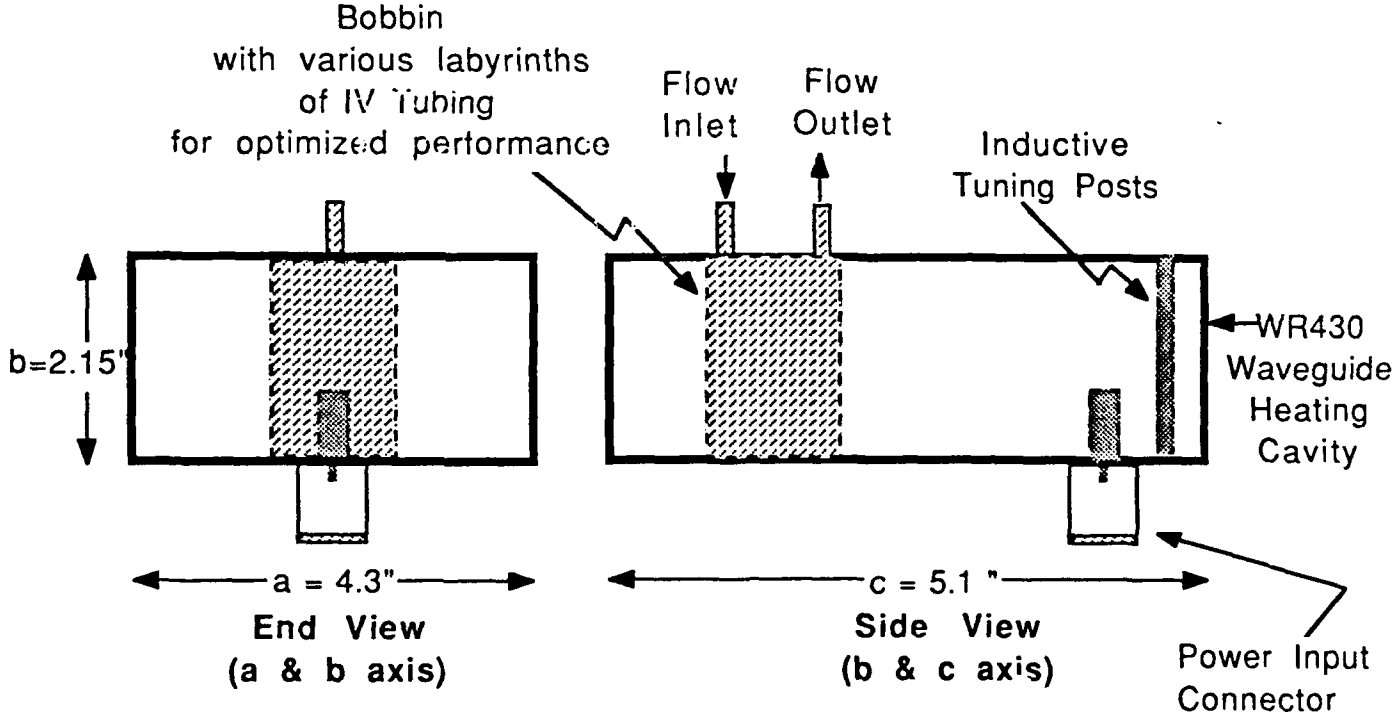


FIGURE 7b. HEATING CAVITY: Optimized Configuration
Several Bobbin & Tuning Configurations were investigated to optimize performance.
Length of tubing in bobbin ranged between 18" and 78".

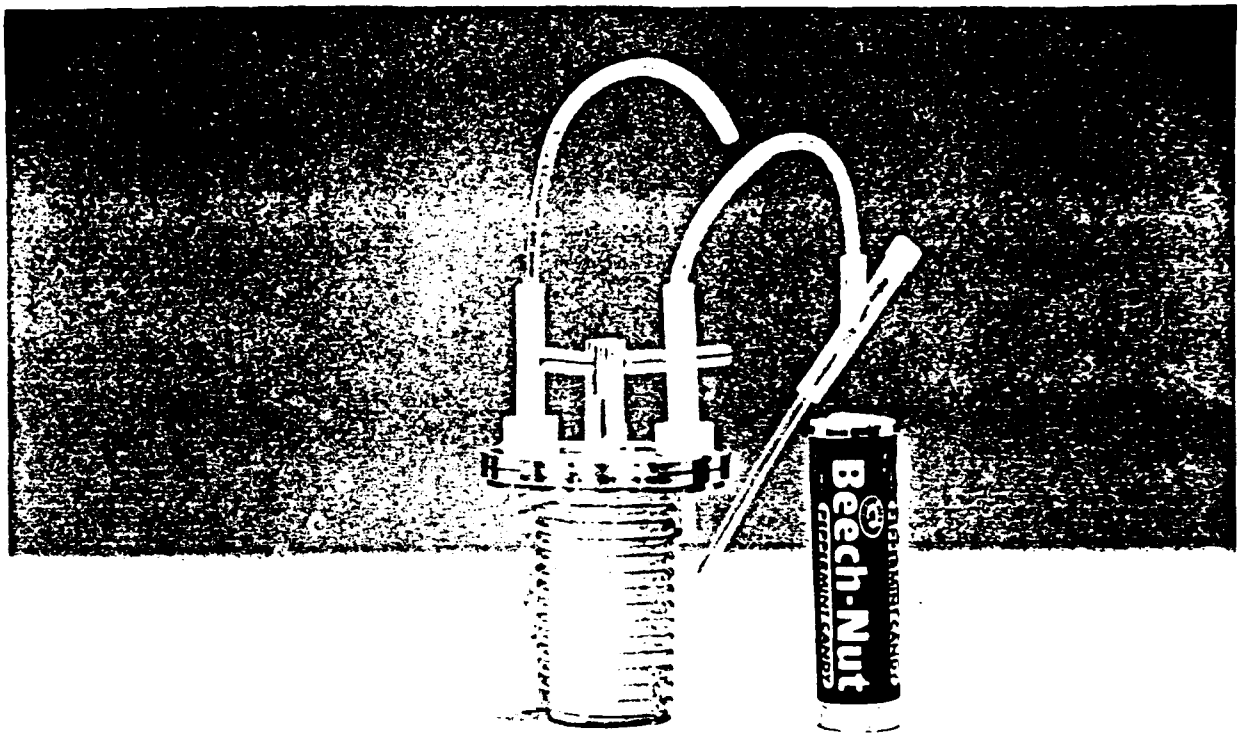


FIGURE 8a. PHOTO OF BOBBIN CONFIGURATION #1

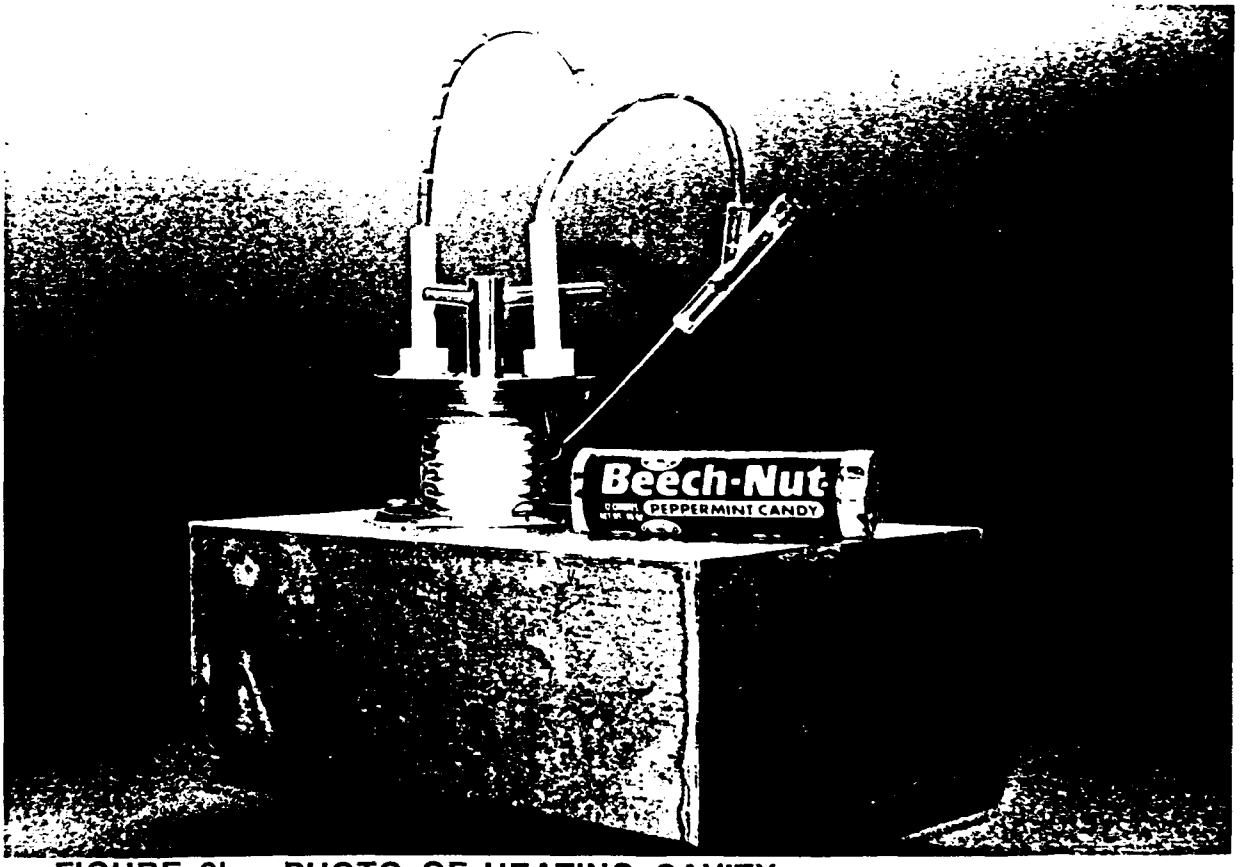


FIGURE 8b. PHOTO OF HEATING CAVITY
WITH BOBBIN INSERTED HALFWAY INTO CAVITY

The heating cavity has been tuned to optimize the Return Loss at 2450MHz as measured by a Scalar Network Analyzer (Wiltron Model 560A). The following procedure was used for tuning the cavity:

(1) The IV Tubing on the bobbin was filled with Saline.
(Note: That Saline approximates the electrical characteristics of blood sufficiently well for the tuning procedure followed here)

(2) The bobbin was inserted into the heating cavity. A threaded metal cap to the bobbin assures that the bobbin is inserted with the same orientation each time the bobbin is inserted.

(3) A Launch from the Power Input connector was extended into the cavity approximately 1.5". The gross tuning of the cavity was accomplished by adjusting the length of this Launch in combination with the next step of optimal positioning of the endplate.

(4) A gross tuning of the heating cavity was accomplished by positioning the Back End Plate(wall in the "a" & "b" plane as shown in **Figure 5.**) along the "c" axis of the heating cavity until the return loss is optimized. This resulted in an inside dimension of 6.38" for the length of the heating cavity along the "c" axis, as shown in **Figure 5.**

(5) Fine Tuning of the Cavity was accomplished using Inductive Tuning Posts positioned between the Power Input Connector and the Back-End Plate. For the follow-on Phase II study, these inductive posts can be eliminated once cavity dimensions are optimized. But for the preliminary work done in the Phase I study, these inductive posts serve as an excellent, quick fine tuning mechanism.

(6) Capacitive tuning with a probe positioned near the bobbin was used in the *first configuration* fabricated in the Phase I study. However, the need for this probe was eliminated by successfully optimizing the length of the cavity in the "c" axis to give a heating pattern that uniformly surrounded the bobbin. Elimination of the capacitive probe also eliminates any "hot-spots" that may be caused by concentrated field patterns at the probe which is in close proximity to the bobbin.

The microwave characterization of this heating cavity is given in **Section 4.1.**

3.2.3 Interface: Generator to Heating Cavity

The interface to the heating cavity utilizes a microwave reflectometer as shown in **Figure 9.** With this configuration, the Reflected Power can be measured using a Power Meter connected as shown in this figure. Knowing the Power Output and measuring the Reflected Power gives an indication of the efficiency of the system in warming blood and IV fluids. This setup is used in the upcoming experiments involving heating of the fluids/blood.

The Waveguide Ferrite Isolator inserted in-line with the waveguide absorbs any abnormal overloads in Reflected Power during the experimental trials.

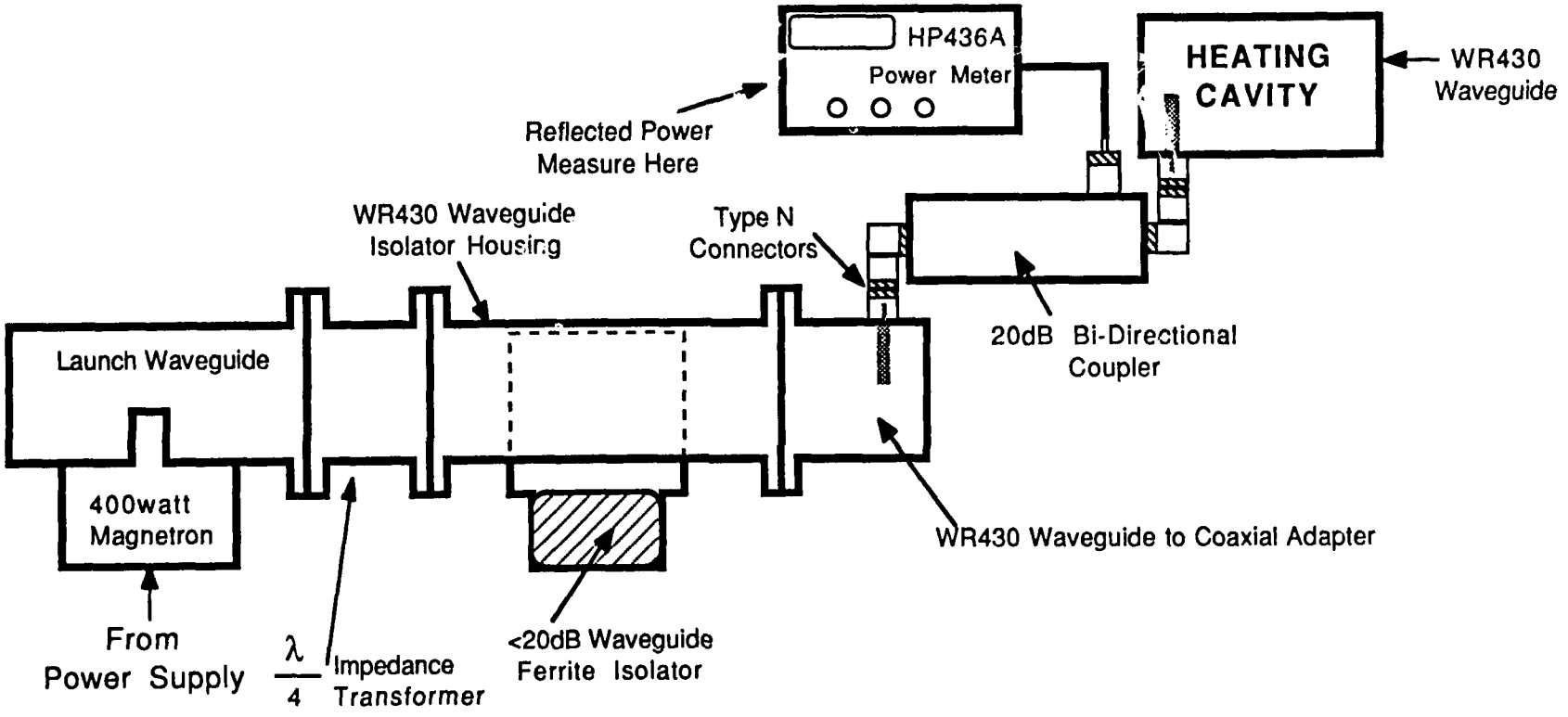


FIGURE 9. WAVEGUIDE INTERFACE FROM MAGNETRON ENERGY SOURCE TO HEATING CAVITY

3.3 Microwave Temperature Monitor

3.3.1 Radiometer

The 4.7 GHz radiometer previously developed at Microwave Medical Systems, Inc. in cooperation with M/A-COM, Inc.[24-28] is used to make the non-invasive temperature measurements of the fluids flowing through the IV tubing. This radiometer is in effect an extremely sensitive radio receiver which, when provided with a highly directional antenna(or transducer) and technique of observation, will provide a reading of power picked up by the antenna. From "black-body" theory, any perfectly absorbing body emits radiation at all frequencies in accordance with Planck's radiation law[32,33]. The distribution of radiation is a function of both the temperature and the wavelength, or frequency. As temperature of the blood(or fluid) increases, the density of the radiation at all frequencies increases. From this viewpoint, infra-red thermography, or radiometry, would appear effective; however, the depth of penetration(which should be referred to as depth of effective emission) becomes the limiting factor. The highest values of radiation density occur in the optical region; nevertheless an appreciable amount of radiation exists in the microwave segment of the spectrum. The radiometer used in this Phase I program is a 4.7 GHz radiometer designed and developed by the co-investigator, Kenneth L. Carr, and used successfully to measure temperature differentials in biological tissue in several studies[24-28]. Development work on the optimization of the radiometer to increase the performance, reduce the size and reduce the production costs is a part of a separate SBIR Phase II program funded by NIH[28,29]. The application in this separate Phase II effort is different(that is, detection of extravasation of intravenously administered drugs by monitoring subcutaneous temperature differentials). However, the resultant radiometer development effort complements the temperature monitoring work required for the blood/fluid warming device. Therefore, in the follow-on Phase II effort for the blood/fluid warming device the development of the temperature monitoring subsystem will have already been underway by Microwave Medical Systems, Inc.(MMS).

The system diagram of the radiometer is shown in **Figure 10**. The results presented in **Section 4.3** show that this radiometer can monitor temperatures with a rapid response rate using the appropriate transducers at the inlet port, outlet port and internal pathway of the heating cavity. Detection of a 10°C change in temperature in less than 1 second with a resolution of 1°C is easily achievable with this system. This rapid response rate is necessary to maintain a safe control of power output by the energy source using the feedback control mechanism. In the Phase II program a multiplexer will be added, as shown in the system block diagram of **Figure 1**, to allow a single radiometer to concurrently monitor temperature at the three designated sites.

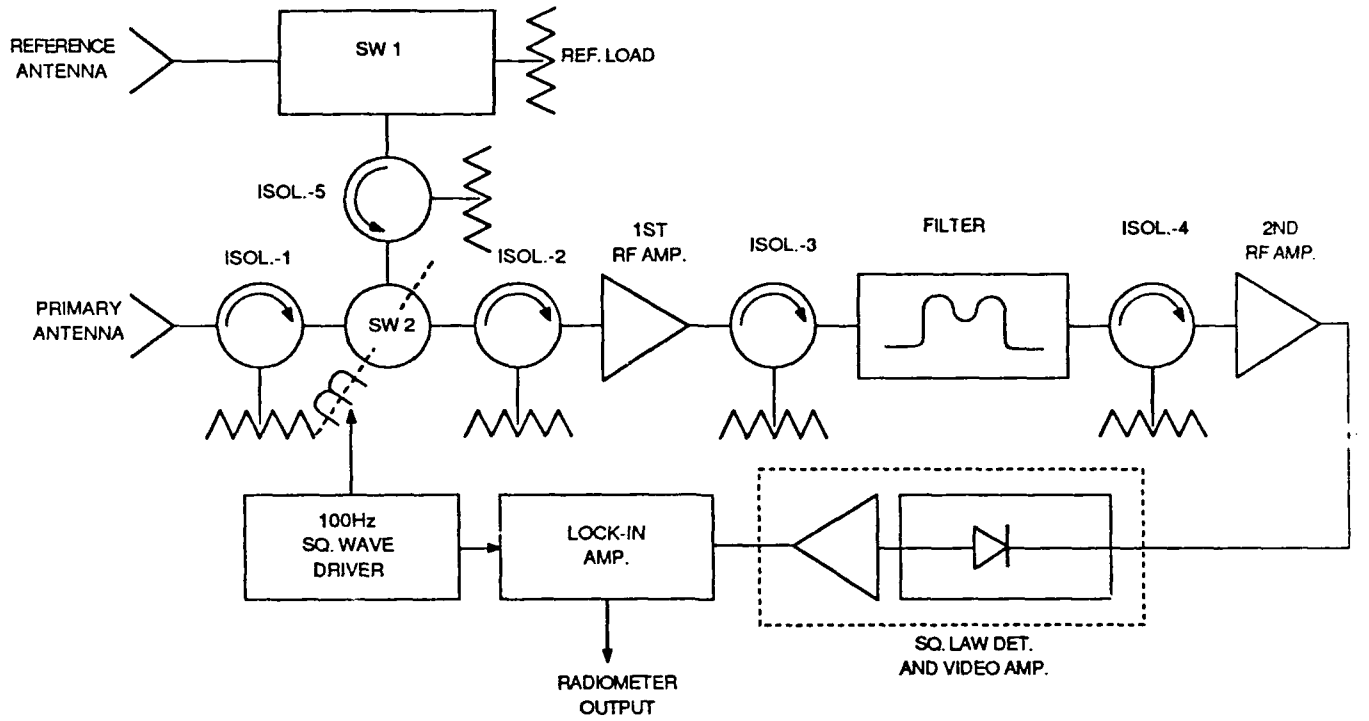


FIGURE 10. 4.7 GHz MICROWAVE RADIOMETER BLOCK DIAGRAM (Temperature Measurement System)

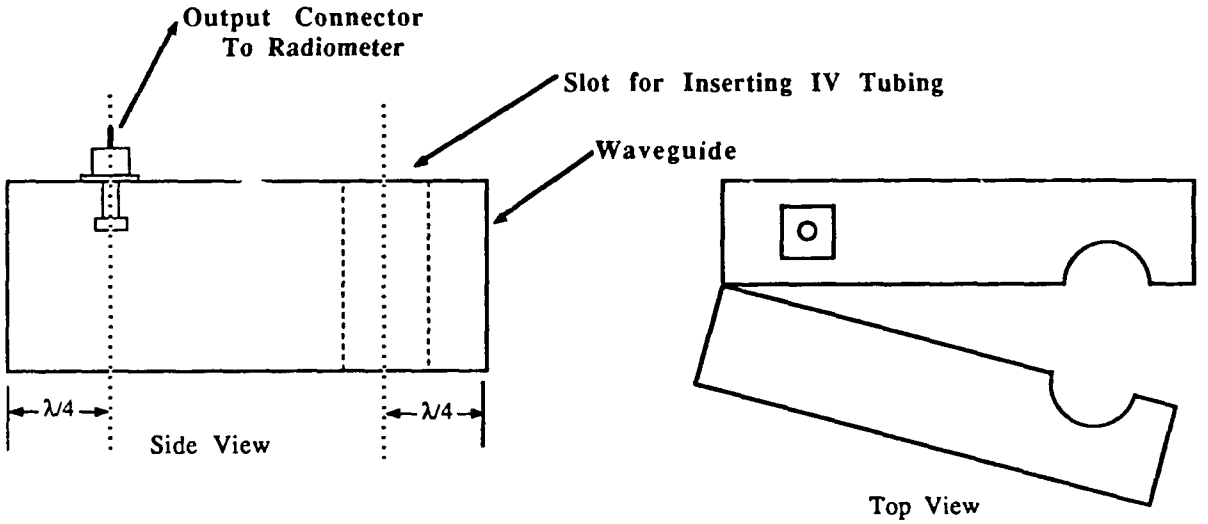


FIGURE 11. SKETCH OF TRANSDUCER DESIGN FOR MONITORING INLET and OUTLET TEMPERATURES (Originally specified by Microwave Medical Systems in Phase I Proposal)

3.3.2 Transducer for Inlet/Outlet Ports

A transducer(that is, a waveguide antenna) that surrounds the tubing was developed and fabricated using the design specified in the Phase I Proposal and sketched in **Figure 11**. The short circuit is placed one quarter wavelength away from the liquid filled tubing. In this particular case, the coaxial probe or launch is located off-center allowing the waveguide to be divided along its length.

Using this design, transducers were fabricated resulting in Configuration#1 shown in **Figure 12**. This design uses metal tubes that surround the IV tubing for a length of approximately 4.5" in either direction, that is at the entrance and exit paths of the transducer. These tubes provide shielding to minimize the influence of external electromagnetic noise on the radiometric temperature measurement of the fluid within the transducer. Work to optimize the design of the transducer for overall size reduction has begun in this Phase I study and will continue in the follow-on Phase II program. The overall length of the entrance and exit shielding tubes has been reduced considerably by fabricating a low profile cylinder of 1.5" diameter and 1.0" height to provide shielding for the same 4.5" length of tubing by winding the tubing in a spiral in side the cylinder. This configuration, Configuration#2, is shown in **Figure 13** and was used successfully to collect the temperature measurement data tabulated in **Section 4.3**. This concept will be further developed in the Phase II study to achieve a shielding cylinder with a much lower profile. Since only one spiral turn of the tubing is required, the cylinder height need only accommodate the outside diameter of the tubing itself.

3.3.3 Transducer for Inside of Cavity

Monitoring the temperature at the inlet and outlet ports of the heating cavity is not sufficient for failsafe performance. For the case where flow stops or is drastically reduced during the infusion process, the temperature of the fluid inside the heating cavity must also be known since heat transfer under these conditions to the outlet transducer will be too slow. The design for a transducer capable of "inside cavity" temperature monitoring was specified in the Phase I proposal and fabricated and tested during the Phase I effort. This transducer monitors the temperature of the fluid along the tubing wrapped around the bobbin-insert inside the heating cavity is coupled into the narrow wall of the heating cavity waveguide. The opening created is small in respect to the transmit frequency and, therefore, does not perturbe the transmit path. The smaller waveguide is cutoff at the transmit frequency isolating the sensitive radiometer from the transmitter. In this Phase I study the spacing of the tubing/bobbin assembly with respect to the wall opposite the detection aperture was determined to optimize radiometric performance. As discussed in **Section 3.2.2** the transducer was placed in a slot on one of the side walls of the cavity(**Figure 5.**). A second configuration placed the transducer in the front-end wall. As presented in **Section 4.3.2**, both of these configurations yielded good results for monitoring temperature of the fluid path inside the heating cavity.

3.3.4 Interface: Transducer to Radiometer

Each of the three transducers are connected to the radiometer via a coax-to-waveguide transition consisting of a SMA connector with a launch extending into the waveguide. This connector/launch configuration is shown for the inlet and outlet transducers in **Figures 11, 12** and **13**; and for the internal monitoring transducer in **Figure 5**. A flexible coaxial cable approximately 4 feet in length is attached to the SMA connector on the transducer and then connected to the input of the radiometer. For the follow-on Phase II effort these coaxial lines would be brought together to a multiplexer switch and then a single cable would be connected to the radiometer.

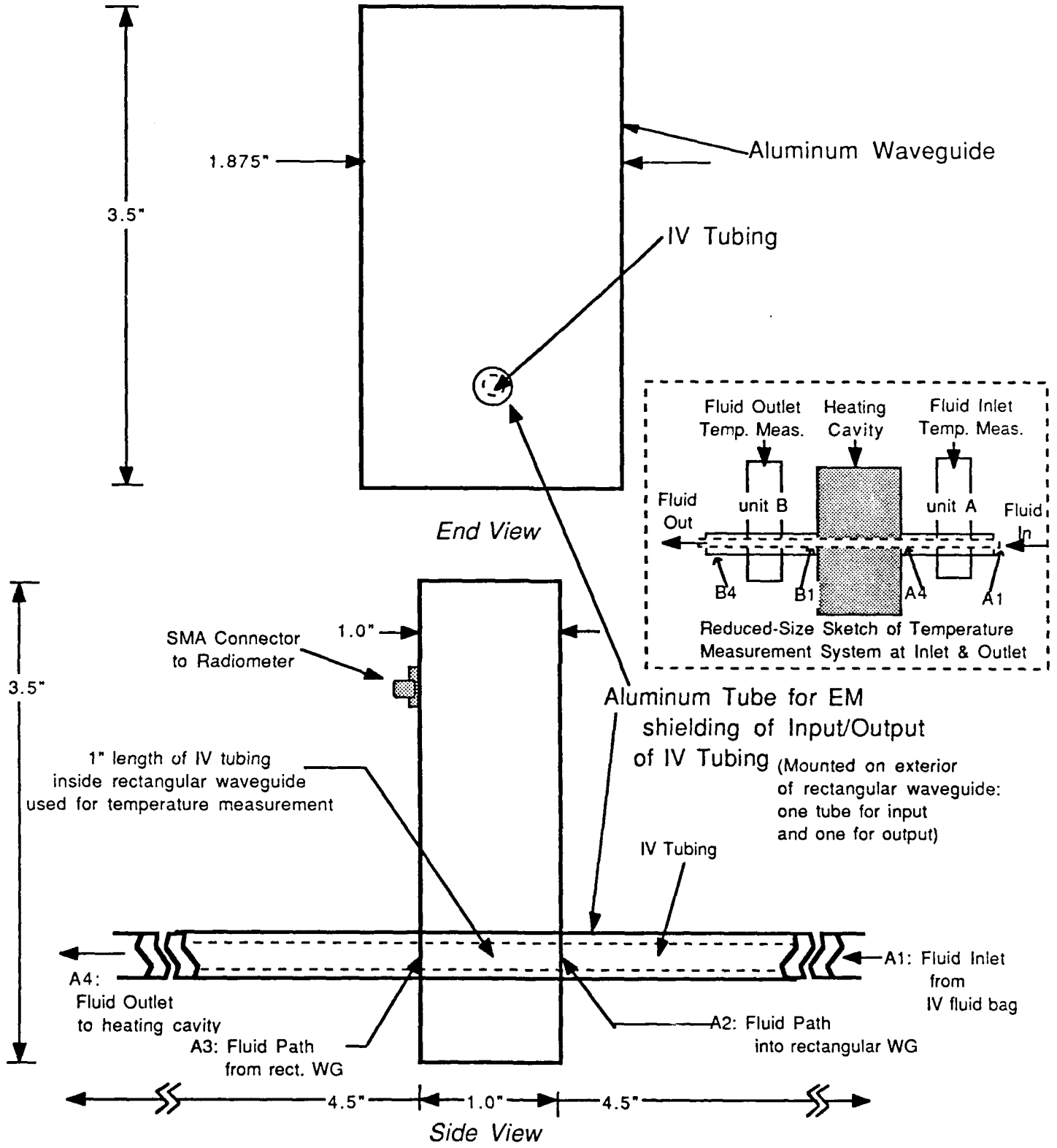


FIGURE 12. INLET/OUTLET TRANSDUCER CONFIGURATION#1

Waveguide temperature measurement scheme with Input/Output EM shielding provided by Aluminum tube, approx. 4.5" long. One Unit (unit A) at entrance to heating cavity. A 2nd Unit (unit B) is required at exit from heating cavity.

NOTE: The above configuration has been fabricated and tested in the laboratory to measure the change of the radiometric signal corresponding to the change of fluid temperature entering at the Fluid-Inlet Port: A1.

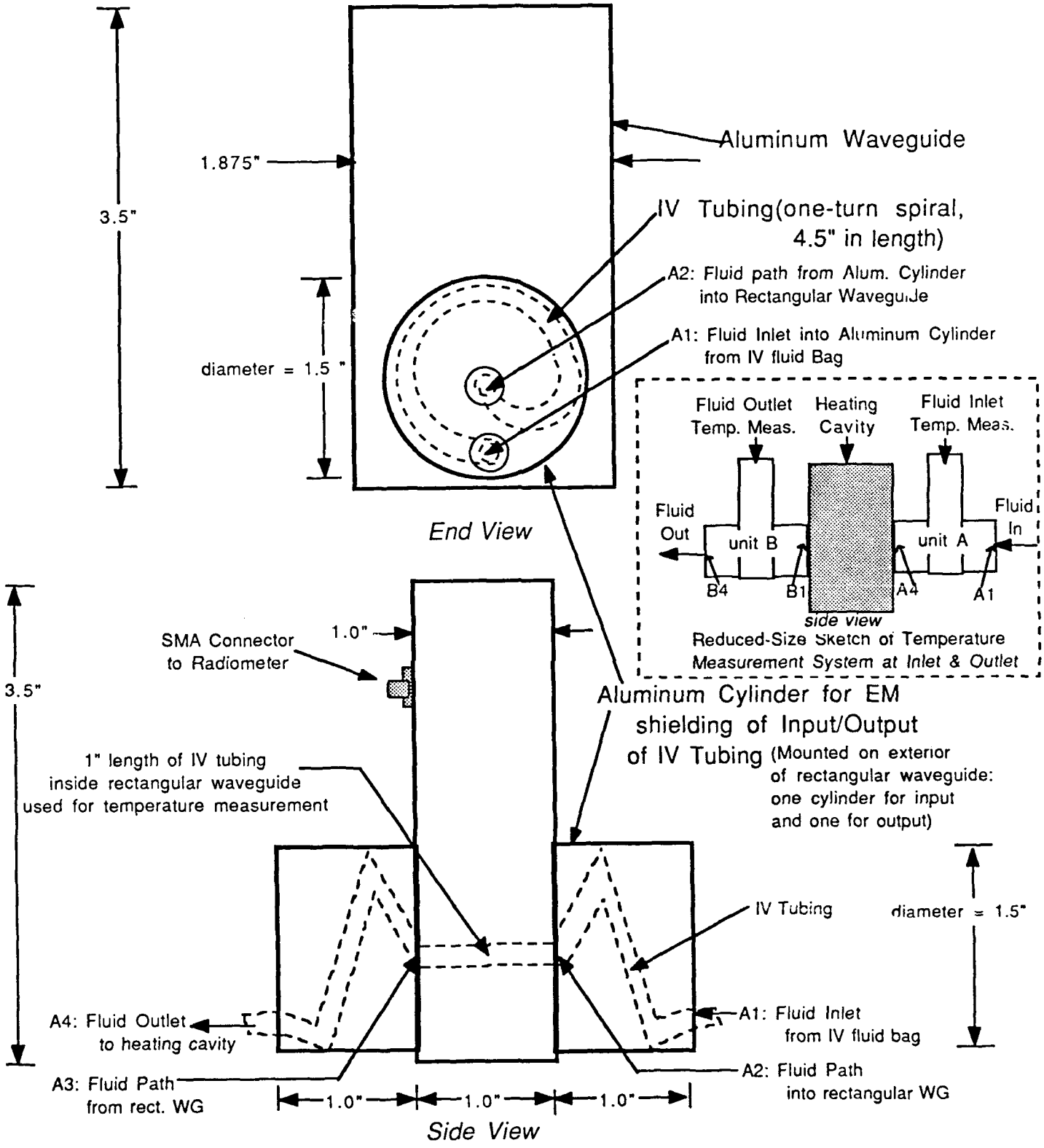


FIGURE 13. INLET/OUTLET TRANSDUCER CONFIGURATION#2

Waveguide temperature measurement scheme with Input/Output EM shielding provided by Cylindrical Path of approx. 4.5". One Unit (unit A) at entrance to heating cavity. A 2nd Unit (unit B) is required at exit from heating cavity.

NOTE: The above configuration has been fabricated and tested in the laboratory to measure the change of the radiometric signal corresponding to the change of fluid temperature entering at the Fluid-Inlet Port: A1.

3.4 Configuration of Phase I Test Fixture

A flow circuit for evaluating *in-vitro* the efficacy of the microwave blood/fluid warming system was setup at the laboratory facilities of our collaborators at the Department of Surgery (Tufts/New England Medical Center). This circuit, shown in **Figure 2**, was configured specifically for this Phase I Study and will continue to be used in the follow-on Phase II Study.

The components of this test circuit are as follows:

- **Reservoir:** For continuous, Multiple-Pass, heating of IV fluids a 1.5 liter bag of IV fluid is used to supply the fluid to the circuit.

  For Single-Pass heating of blood a 60 ml syringe is used to supply the blood to the circuit.

- **Pump:** For continuous, Multiple-Pass, operation a Biomedicus Pump is used to pump the IV fluid or blood thru the circuit. This Pump has flow rates of up to 5 liters per minute with a resolution of about 25 ml/min. The particular pump that we are using is one that has been used on patients in the opearting room at the Department of Surgery at Tufts New England Medical Center. It is a constrained vortex type of Pump. The pump head has a series of vaneless rotor cones which, when spinning, impart a circular motion to the blood, generating centrifugal force and subsequently flow and pressure.

  For Single-Pass operation a Cordis Injector Syringe Pump is used to inject blood into the system at rates ranging from 250 ml/min to 500 ml/min.

- **Cooling Heat Exchanger:** A conventional, counter current, heat exchanger is next in line with pump. This heat exchanger is used to cool down the fluid/blood to a known temperature prior so that the fluid/blood temperature can be controlled as it flows into the microwave heating cavity.

- **Microwave Heating Cavity:** The microwave heating cavity, as described in Section 3.2.2, is essentially waveguide with an "insert" of IV tubing placed through the waveguide interior. This "insert" is a bobbin of IV tubing wound in a spiral configuration and optimized for uniform absorption of the microwave energy. The fluid/blood flows from the cooling heat-exchanger, into the inlet port of the heating cavity, through the heating cavity, out of the outlet port of the heating cavity. From the heating cavity's outlet port, the flow can be directed back to the Reservoir or to the Sample Collection Port via a valve.

- **Sample Collection Port:** After the fluid/blood flows out of the heating cavity there is a "Y" junction. The main branch of this "Y" junction leads back into the reservoir bag. The secondary "Y" branch is normally clamped. When this clamp is opened, the fluid/blood can be collected in a syringe. This method is used to collect control and heated samples of the fluid/blood for subsequent laboratory analysis.

- **Microwave Energy Source:** The microwave energy to the heating cavity is supplied by through use of a magnetron operating at 2450 MHz as described in **Section 3.2.** It is connected to the heating cavity through the use of a waveguide-to-coaxial transition.

- **Temperature Probes:** Inlet and outlet temperatures to and from the heating cavity are measured through the use of a Fluoroptic Thermometry system, manufactured by Luxtron, Inc. This system is used only to verify these temperatures in the test circuit and are not intended to be part of the final commercial system. The fluoroptic probes are non-perturbing to electromagnetic fields and thus can be inserted anywhere near or within the heating cavity to make temperature measurements. These probes are invasive, that is, placed inside the tubing carrying the fluid/blood. However, at the inlet and outlet ports of the heating cavity, these probes are placed as unobtrusively as possible. They are inserted into the pathway through a "Y" connection the outlet of one of the "Y" legs is the main circuit, the second "Y" leg is sealed with a rubber, self-sealing, membrane thru which the probe is placed. The tubing within the heating cavity is of course common IV tubing. Thus, any temperature measurements made within the IV tubing pathway will only give a relative indication of temperature.

- **Tubing:** The tubing inside the heating cavity is common IV tubing. The tubing throughout the circuit can be configured with any diameter tubing from 3/8" inside diameter to 3/32" inside diameter IV tubing.

3.5 In-Vitro Experimental Trials

Following the Work Plan specified in the Phase I proposal, the efficacy of the in-line microwave warming device was determined by examining the differences in constituency of blood samples heated *in-vitro* with the device from that of unheated samples obtained from the same donor. Heating levels were sufficient to raise the temperatures of the samples from refrigeration to normal body temperature.

Testing of IV fluid constituency changes due to microwave heating was not a part of the original Work Plan presented in the Phase I proposal because sufficient evidence has previously been obtained by other investigators on the effects of microwave heating on bulk bags of these fluids[7]. However, there was time in the Phase I study to perform a limited set of experiments. Results obtained here confirm those results in a study by Anshus which shows that microwave heating produces no significant changes in fluid constituency[7]. More extensive analysis of IV fluids heated by the microwave system will be performed in the follow-on Phase II program.

3.5.1 IV Fluid Warming

These tests were performed to examine any change in the IV Fluid due directly to the microwave heating or indirectly by plasticizing of the IV tubing. For these tests, IV fluids were recycled through the system at rate of 150 ml/min for 5 minutes and at 120 ml/min for 10 minutes using the 1.5 liter reservoir bag as a recirculating supply(see **Figure 2** for test fixture configuration). The Biomedicus Pump was used to control fluid flow rate. Microwave energy supplied to the heating cavity was 400 watts. As shown in the test circuit(**Figure 2**), samples were continuously cooled by a conventional water-bath heat exchanger placed in-line before the microwave heating cavity.

At the 150 ml/min flow rate the fluid was heated by the microwave warming system from 2°C to 37°C, yielding a $\Delta T = 35°C$.. At the 120 ml/min flow rate the fluid was heated from 3°C to 46°C, yielding a $\Delta T = 43°C$. These slow flow rates were used so that any changes in fluid constiuency due to plasticizing would be maximized by the high temperature elevations($\Delta T = 35°C$ & 43°C).

Two IV Fluids were tested: 0.9% Normal Saline and Lactated Ringer's. Three types of control samples were collected for each IV fluid: (1) Unheated and uncirculated IV fluid taken directly from the bottle; (2) Cool IV fluid circulated unheated through the test circuit; (3) IV fluid heated by a conventional water-bath heat exchanger and circulated through the test circuit. The specific test trials used for this experiment were as follows:

IV FLUID#1: 0.9% SALINE

- **SAMPLE#1a:** Control *(taken directly from bottle)*
  - Heat Source: none
  - ΔT: none
  - Circulation: none

- **SAMPLE#1b:** Control *(unheated, circulated)*
  - Heat Source: none
  - ΔT: none (kept at 2°C by cooling water bath)
  - Circulation: 10 minutes @ 150 ml/min

- **SAMPLE#1c:** Control *(heated, circulated)*
  - Heat Source: conventional water bath
  - ΔT: none (kept at 40°C by heat exchanger)
  - Circulation: 40 minutes @ 150 ml/min

- **SAMPLE#1d:** Microwave Heat Trial #1 *(heated, circulated)*
  - Heat Source: Microwave Fluid Warmer
  - ΔT: 35°C (Tinlet = 2°C, Toutlet = 37°C)
  - Circulation: 5 minutes @ 150 ml/min

- **SAMPLE#1e:** Microwave Heat Trial #2 *(heated, circulated)*
  - Heat Source: Microwave Fluid Warmer
  - ΔT: 35°C (Tinlet = 2°C, Toutlet = 37°C)
  - Circulation: 5 minutes @ 150 ml/min

IV FLUID#2: LACTATED RINGER'S

- **SAMPLE#2a thru 2e: same as for SAMPLE #1a thru 1e above**

3.5.2 Blood Warming

Samples of fresh human blood drawn from paid volunteers at the Department of Surgery of New England Medical Center were used for these experiments. Using fresh blood eliminates the variables in constituency due to storage and handling of blood-bank blood; and therefore control parameters are well established. Prior to these experiments, approvals from the Human Experimentation Review Committee were obtained as required(see **Appendix**).

The Cordis Injector Syringe Pump was used to control fluid flow rate as shown in **Figure 2.** Microwave energy supplied to the heating cavity was 400 watts. The protocol followed for these experiments was as follows:

- **Obtain written consent of volunteer**

- **Draw approximately 120 ml of blood from volunteer**
  Needle used: 19 gauge "butterfly"
  Blood sample drawn into two 60 ml syringes(Supply#1 & Supply#2)

- **Place blood samples(in syringes) into water bath for cooling**
  Starting temperatures range between 8°C and 16°C

- **Load Injector Syringe and Place in Syringe Pump of Test Circuit**

- **BLOOD SAMPLE a: Control(unheated) Sample**

Collect an unheated sample of blood

- Pump contents of Injector Syringe at the rate of 300 ml/min through Test Circuit with the Microwave Power Off
- Collect 15 ml in test tubes for lab analysis.
  Collect 45 ml in Recycling Syringe
- Refill Injector Syringe with:
  Contents from Recycling Syringe + Supply Syringe#1&#2

- **BLOOD SAMPLE b: One-Pass Sample** *(blood heated 1 time)*

Collect a sample of blood heated one-time

- Pump contents of Injector Syringe at the rate of 300 ml/min through Test Circuit with the Microwave Power On at level of 400 watts
- Collect 15 ml in test tubes for lab analysis.
  Collect 45 ml in Recycling Syringe
- Refill Injector Syringe with:
  Contents from Recycling Syringe + Supply Syringe#1&#2

- **BLOOD SAMPLE c: Two-Pass Sample** *(blood heated 2 times)*

Collect a sample of blood heated two-times

- Pump contents of Injector Syringe at the rate of 300 ml/min through Test Circuit with the Microwave Power On at level of 400 watts
- Collect 15 ml in test tubes for lab analysis.
  Collect 45 ml in Recycling Syringe
- Refill Injector Syringe with:
  Contents from Recycling Syringe + Supply Syringe#1&#2

- **BLOOD SAMPLE d: Three-Pass Sample** *(blood heated 3 times)*

Collect a sample of blood heated three-times

- Pump contents of Injector Syringe at the rate of 300 ml/min through Test Circuit with the Microwave Power On at level of 400 watts
- Collect 15 ml in test tubes for lab analysis.
  Collect 45 ml in Recycling Syringe
- Supply Syringes#1 & #2 are depleted at this point

- **Analyze blood samples a,b,c & d using standard tests**
  (Clinical Hematology Laboratory at New England Medical Center)

- **Vary Protocol to obtain samples at different flow rates**
  - Collect some Samples at flow rates other than 300 ml/min to obtain variations in temperature elevation of blood with the power source held constant at 400 watts.

4.0 RESULTS

4.1 Microwave Characteristics of Heating Cavity

Microwave characteristics of the heating cavity have been measured using the Wiltron 560A Scalar Network Analyzer. For each iteration in the shape and size of the heating cavity and its associated bobbin-insert of IV tubing, the Return Loss and Insertion Loss were measured. The Return Loss is a two-way measurement, that is, the ratio of power reflected to the power transmitted. The Insertion Loss is a one-way measurement that indicates the amount of Power absorbed in one direction by the load.

Since the Return Loss represents the ratio of microwave energy reflected by the load *(in this case the bobbin of IV tubing filled with fluid)* within the heating cavity at a given frequency, the optimum configuration of heating cavity can be found by maximizing the Return Loss at the operating frequency of 2450 MHz. From the Return Loss the Power Ratio of the device can be derived using the following relationship:

$$\textbf{Return Loss} = -10 \log \textbf{Power Ratio}$$

$$\text{where } \textbf{Power Ratio} = \frac{P_{reflected}}{P_{Input}}$$

For example, the measured Return Loss of the Original Heating Cavity was 20db for a bobbin filled with 0.9% Normal Saline. This is equivalent to a Power Ratio = .01. Expressing this as a percentage, we see that %Power Reflected is 1% and therefore the %Power Absorbed is 99%.

Starting with the original design as specified in the Phase I proposal, a heating cavity was fabricated as shown in **Figures 5** and **7**. The bobbin-insert, shown in **Figures 6** and **8**, used for this original configuration had a coil of 78 inches of IV tubing wrapped around the length of the bobbin's cylindrical core. Although the Return Loss, as shown in **Table 1**, for this configuration, was acceptable, improvements were necessary to increase the Insertion Loss.

The final configuration of the heating cavity and associated IV tubing bobbin insert is shown in **Table 1** under the column: "OPTIMIZED CONFIGURATION". This configuration was used to heat the samples of fluid in the experimental trials conducted in this Phase I study. The Insertion Loss of 8 dB represents a dramatic increase in performance over the original configuration and indicates that the microwave energy is absorbed more uniformly and efficiently over the entire length of the coil of IV tubing on the bobbin.

To determine the performance of the heating cavity for other IV fluids besides Saline, the Return Loss was measured for Lactated Ringer's, 5% Dextrose Ringer's and 5% Dextrose Water. These values are listed in **Table 2** for the heating cavity with and without the radiometric temperature measurement transducer in place. The results are virtually the same as saline except for 5% Dextrose Water. In the follow-on Phase II study, modifications can be made to the cavity to allow a better match for this fluid. An important observation in the results listed in **Table 2** is that the performance of the heating cavity is virtually uneffected by the presence/absence

of the temperature measurement transducer element placed within one wall of the heating cavity as shown in **Figure 5.** For example the difference between 26.7 dB and 30 dB for the Return Loss of 5% Dextrose Ringer's with and without the temperature measurement transducer is less than 0.5%.

PARAMETER @ 2.45 GHz	ORIGINAL CONFIGURATION	OPTIMIZED CONFIGURATION
Heating Cavity Size	6.25" x 4.3" x 2.15"	5.1" x 4.3" x 2.15"
Bobbin Size	1.2" diam x 2" height	1"diam x 2.1"height
IV Tubing Length (on bobbin)	78"	19"
Volume of Fluid (in tubing coiled around bobbin)	10 ml	2.5 ml
Insertion Loss (without tuning posts)	3 dB	8 dB
Return Loss (with tuning posts)	20 dB	28 dB
% Power Absorbed	99%	99.5%

TABLE 1. Microwave Characteristics of Heating Cavity with IV Tubing Bobbin Insert filled with 0.9% Saline

IV FLUID	RETURN LOSS with temperature transducer	RETURN LOSS without temperature transducer	BANDWIDTH
0.9% Normal Saline	27.5 dB	28.2 dB	15dB: 200MHz
Lactated Ringer's	23.5	25.2	15dB: 200MHz
5% Dextrose Ringer's	26.7	30	15dB: 200MHz
5% Dextrose Water	9.8	10.4	8dB: 400MHz

TABLE 2. Return Loss of Heating Cavity with IV Tubing Bobbin Filled with IV Fluids.
Measurements made with & without temperature monitoring transducer in place within one wall of heating cavity.

4.2 Heating Capacity of System

To determine the heating capacity of the system empirically, experiment trials were conducted to measure the temperature elevation of cool fluids flowing through the system. Using the test circuit shown in **Figure 2**, cool 0.9% saline was supplied to the inlet of the heating cavity and heated using the 400 watt energy source operating at 2450 MHz. The results of these trials, listed in Table 3, show a favorable comparison with the expected or calculated temperature elevation.

The theoretical temperature elevation of fluids heated with the 400 watt microwave energy source at given flow rates is given by the following relationship:

$$P = k \frac{Q}{60} \rho \; C \; \Delta T$$

where:

- **P** = Power in watts, 1 watt = 1 joule/sec
- **k** = 4.184 joules/calorie
- ρ = Density (= 1 gm/ml for water, = 1.05 gm/ml for blood)
- **C** = Specific heat in calories/gm °C (= 1 cal/gm °C for water) (= 0.93 cal/gm °C for blood)
- ΔT = Temperature difference in °C; $\Delta T = T_{output} - T_{input}$
- **Q** = Volumetric Flow Rate in ml/min; Q/60 = Flow Rate in ml/sec

For Example:

@150 ml/min and 400 watts of heating power, ΔT becomes:

$$\Delta T = \frac{P}{k \frac{Q}{60} \rho \; C} = \frac{400}{4.184 * \frac{150}{60} * 1 * 1}$$

$$= 38.2°C$$

As shown above, the calculated temperature elevation for a flow rate of 150 ml/min is 38.2°C. This compares with an actual measured temperature difference of 37°C as shown in **Table 3**. A sample of temperature elevations measured using several different flow rates are also listed in **Table 3**. Each of these empirical measurements compares very favorably with the calculated values. It should be noted that the flow rates were measured using the flow meter on the Biomedicus Pump as shown in **Figure 2**. Since Flow Rates below 500 ml/min are difficult to control and measure with the Biomedicus Pump, the flow rate values listed in **Table 3** should be considered as approximations(i.e., ± 10%).

Further experiments were conducted to determine the consistency of maintaing a constant temperature elevation for a given flow rate. For these experiments Ringer's Lactate was used. Several trials were conducted at flow rates ranging from 110 ml/min to 180 ml/min. Results are summarized in **Table 4.**

These results were conducted at relatively low flow rates to create a "worst-case" evaluation of the performance of the microwave warmer. At these low flow rates, the temperature rise between input and output temperatures are quite high. For example, the calculated temperature rise for fluid flowing at 120 ml/min when heated by a 400 watt source is approximately 48°C.

Table 4 shows the observed input versus output temperatures at flow rates ranging from 110 ml/ min to 180 ml/min. Actual flow rates are difficult to determine since the Biomedicus Pump used to pump the fluid through the circuit is inconsistent below 500 ml/min. However, what is important is that once a flow rate is established, the ΔT remains constant. This was the case as shown by actual data in the chart.

The last trial shown on Table 4 was conducted to give a preliminary indication of any "hot-spots" that may be present in the prototype heating cavity. This was done by starting with a flow rate of approximately 120 ml/min and gradually reducing the flow rate so that the temperature elevation, ΔT, would rise proportionally. With elevations of temperature as high as 48°C, any "hot-spots" (i.e., areas of heating that are 5°C to 10°C above the average output temperature)within the system would be more pronounced and readily detected. These "hot-spots", if present when output temperatures are in the range of 55°C to 60°C, would in fact result in the deformation or softening of the PVC IV tubing. No such "hot-spots" were detected in our prototype heating cavity. When fluid at an input temperature of approximately 5°C to 6°C was introduced into the system at 120 ml/min, output temperatures ranging from 46°C to 58°C were observed as the flow rate was reduced; visual examination of the tubing within the heating cavity showed no damage.

TRIAL#	FLOW RATE	Measured Temperature			Calculated Temp
		Tinlet	Toutlet	ΔT = To -Ti	ΔT
	ml/min	°C	°C	°C	°C
S-3	150	5	42	37	38.2
S-12	200	10	37	28	28.7
S-16	250	4	29	25	22.9
S-19	342	22	40	18	16.8
S-20	411	22	37	15	14.0
S-22	500	4	16	12	11.4

TABLE 3. Temperature Elevation, ΔT, of 0.9% Normal Saline for Different Flow Rates
Flow Rates are determined by Flow Meter on BioMedicus Pump and are accurate to approximately ±10% at Flow Rates below 500 ml/min.
Measured Temperatures are sampled with Luxtron Fluoroptic Thermometry System and represent average Temp over 5 seconds.

ELAPSED TIME seconds	TRIAL#RL-1 Flow rate = approx. 140 ml/min Reflected Power = 8 to 12 watts		TRIAL#RL-2 Flow rate = approx. 125 ml/min Reflected Power = 6 watts		TRIAL#RL-3 Flow rate varied: ≈125 ml/min to 100 ml/min Reflected Power ≈4.4 watts		
	INPUT TEMP °C *(avg for 5 secs)*	OUTPUT TEMP °C *(avg for 5 secs)*	INPUT TEMP °C *(avg for 5 secs)*	OUTPUT TEMP °C *(avg for 5 secs)*	INPUT TEMP °C *(avg for 5 secs)*	OUTPUT TEMP °C *(avg for 5 secs)*	
t=0 (start)	4.0	37.6	4.1	45.4	6.3	46.6	<--start≈125 ml/min
5	4.3	37.9	3.9	45.1	6.2	50.2	
10	4.2	37.7	3.9	44.7	6.2	50.8	
15	4.2	38	3.8	45.2	6.1	52.5	
20	4	37.9	3.6	45	6	54.5	
25	4.2	38.1	3.8	45	6	54.5	
30	4.3	37.9	3.7	44.7	6	52.7	
35	4.2	38	3.5	44.8	5.9	52.6	
40	4.1	37.9	3.7	44.7	5.6	52.2	
45	4.1	38	3.5	44.9	5.7	57.7	
50	4.3	38.1	3.6	44.6	5.4	58.1	
55	4.1	37.9	3.4	44.8	5.4	58	
60	4.2	37.8	3.4	45	5.3	58.4	<--end≈100 ml/min

TABLE 4 CONSISTENCY OF MICROWAVE HEATING FOR A CONSTANT FLOW RATE & CONSTANT INLET TEMPERATURE

Temperature at Heating Cavity Outlet Remains Constant

Input versus Output Temperature observed at in/out ports of heating chamber
Ringer's Lactate Solution flowing through IV tubing of bobbin
Temperatures measured using Luxtron fluoroptic temperature measurement system

4.3 Temperature Monitoring: Resolution & Response Time

Tests were conducted in our engineering laboratory to characterize the sensitivity of the non-invasive radiometric temperature measurement system for measuring the temperature of fluids within IV tubing. Saline(0.9% Normal) was the fluid used for these tests. Both the transducer used for measuring Inlet/Outlet temperatures and the transducer used for measuring temperatures inside the heating cavity were characterized. Characterization involved the measurement of two parameters:

Resolution: This is the smallest increment of scale to which the measurement can be resolved. For the radiometer output this is related to the signal-to-noise ratio of the voltage signal. Since the last stage of the radiometer is an integrator, the time constant, τ, directly affects this resolution. As the time constant is increased, the output signal will be integrated(averaged) over a longer time and therefore the signal-to-noise ratio will increase. As the signal-to-noise ratio increase, the resolution improves.

Response Time: This is the time that it takes the radiometer to reach 90% of its final level for an incremental temperature change. As the time constant, τ, is decreased, the output signal will be integrated(averaged) over a shorter time and therefore the response time will decrease. However, a decrease in the time constant will decrease the signal-to-noise ratio increase, and thus decrease the resolution.

4.3.1 Inlet Outlet Temperature Monitoring

Characterization of the Inlet/Outlet Temperature Monitoring Transducers($\mathbf{Xducer}_{I/O}$) was performed for the configuration shown in **Figures 12 & 13** and explained in **Section 3.3.2.** A flow rate of 350 ml/min was chosen as a representative value for testing purposes. It is projected that use of the Microwave IV Fluid and Blood Warmer device will be for warming fluid flowing at rates of between 50 ml/min and 500 ml/min

Temperature Resolution provided by $\mathbf{Xducer}_{I/O}$, when connected to the 4.7 GHz radiometer, was determined by measuring the radiometer output corresponding to the temperature of saline in IV tubing flowing through the transducer as shown in **Figure 12.** The saline was pumped at the rate of 350 ml/min into the inlet port of the transducer from a large heated bath containing 0.9% Normal Saline.

The temperature of the saline bath was regulated by a heater capable of maintaining a constant bath temperature with a variation of less than 0.05°C. The bath temperature was then raised in increments of 1°C and at each incremental temperature the voltage output of the radiometer was recorded.

Response Time for detecting abrupt changes in fluid temperature of the radiometric system for $Xducer_{I/O}$ was determined as follows:

1. IV tubing threaded thru $Xducer_{I/O}$ shown in **Figure 12**
2. Prior to the Input to $Xducer_{I/O}$, the IV tubing is split by a "Y" junction. One branch of the "Y" placed in a reservoir of Saline at a temperature of **T1** ≈ 38°C and the second branch placed in a reservoir of Saline at a temperature of **T2** ≈ 24°C.
3. The temperature of Fluid flowing into $Xducer_{I/O}$ at 350 ml/min was switched between **T1** and **T2** by clamping and opening the appropriate branch of the "Y" junction.
4. Temperature changes, ΔT, of approximately 14°C were achieved using this mechanism.
5. The length of time was measured for the radiometer to change 90% of its final output level after the fluid temperature was switched(Step 3). Step 5 was repeated for different values of radiometer integration time constant, τ .

Since the resolution and response time of the radiometry system is related to the integration time constant, τ , at the output of the radiometer, test were conducted for several values of τ. These results are listed in **Table 5**. There is a trade-off of response time versus sensitivity; the final system design will be determined by considering these trade-offs. These Phase I results will provide data to make an intelligent choice of these tradeoffs for the follow-on Phase II program. The resolution is determined by measuring the noise (in the form of peak-to-peak voltage variations) of the radiometer output at a specific constant fluid temperature.

For determining Temperature Resolution, data was recorded at the radiometer output for fluid temperatures at 1°C increments between 34.0°C and 38.0°C. A sample of data for an integration time constant of τ = 1 sec is shown in **Figure 14**. This data yields the following relationship:

For τ = 1 sec:

ΔV of 0.4v(radiometer output) *equivalent to* ΔT of 1°C(fluid temperature)

noise of 0.08v(radiometer output) *equivalent to* $T_{resolution}$ of 0.25°C(fluid temperature)

Similar data was recorded for several integration time constants; these data are summarized in **Table 5**.

For determining Response Time, data was recorded at the radiometer output while the fluid inlet temperature was switched between **T1** and **T2**. Results show that 90% of the maximum change in temperature detected by the radiometric system occured in approximately 2 seconds with the radiometer time constant at τ = 0.3 secs. With the time constant at τ = 0.1 secs, 90% of the maximum temperature change detected occured in approximately 1 second. Response Times recorded for different integration time constants are summarized in **Table 5**. The determination of the exact response time is limited by the fact that the water temperature from a newly selected branch of the "Y" junction will mix with water already in the tubing beyond the "Y" junction. Thus, the response times are in fact, "worst-case" values limited by the switching mechanism of the experimental setup.

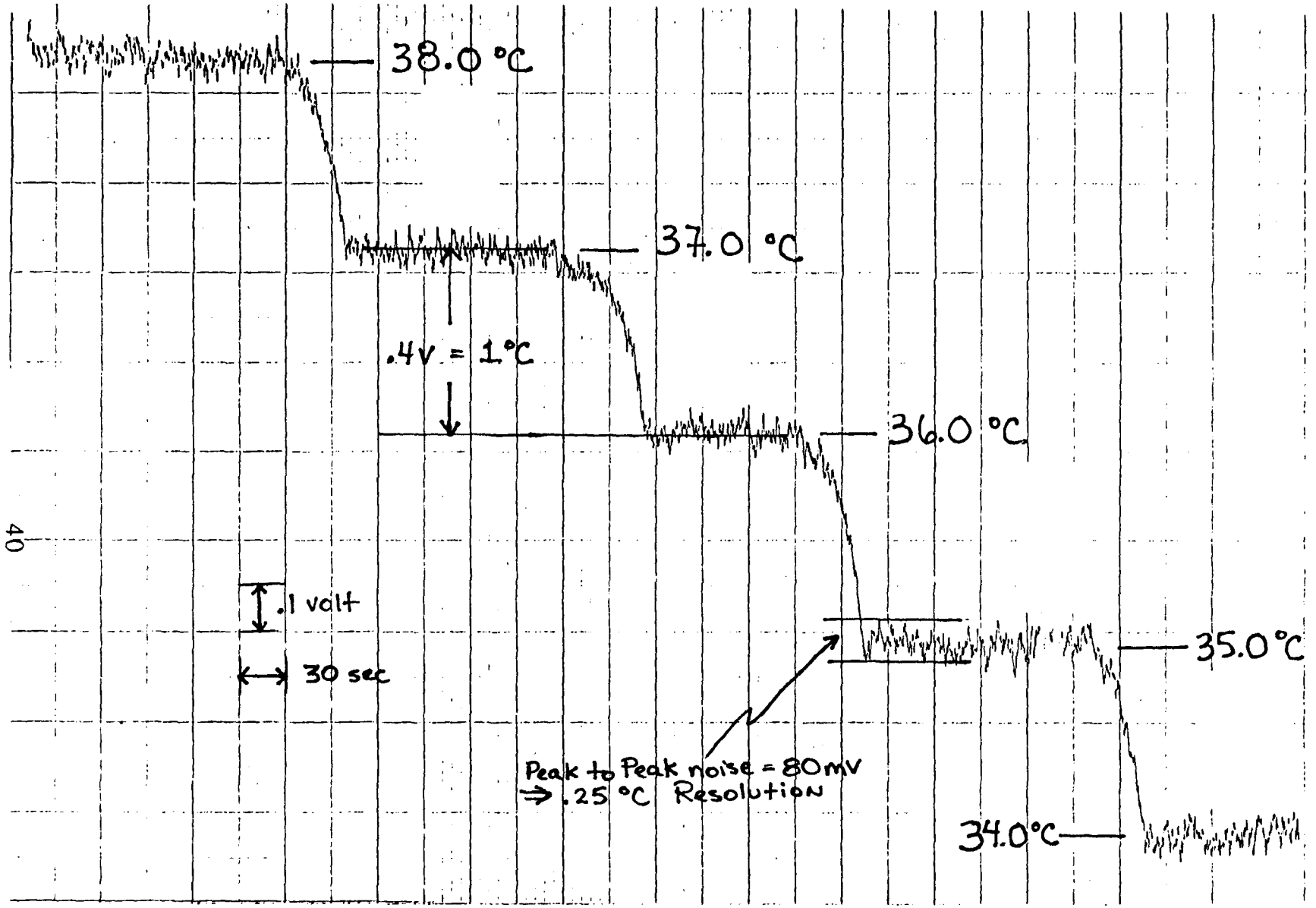


FIGURE 14 **Sensitivity of Radiometric Output to Temperature Changes of Fluid flowing thru Waveguide Temperature Sensing Element: $Xducer_{I/O}$**

PROCEDURE:
1. IV Tubing threaded straight thru $Xducer_{I/O}$ element
2. Fluid Temperature changed in ≈1°C increments
3. Avg fluid temperature measured along length(≈1") of IV tubing @ Input/Output ports

Using the calculation(shown with Table 5) of fluid volume passing through the transducer at a flow rate of 350 ml/min we see that a volume of 6 ml passes through the 1 inch of IV tubing in the $\mathbf{Xducer}_{I/O}$ in 1 second(or 12 ml in 2 seconds). Therefore, 90% of the temperature change is observed after only 6 ml passes through the $\mathbf{Xducer}_{I/O}$ with the radiometer time constant at τ = 0.1 secs (or 12 ml for τ = 0.3 secs). These results are very encouraging, particularly when considering that these response rates represent "worst-case" values, as mentioned above.

RADIOMETER Integration Time Constant τ , seconds	SIGNAL NOISE peak-to-peak voltage millivolts	RESOLUTION °C	RESPONSE TIME time to achieve 90% of final level seconds
1.0	80 mv	0.25	2.5
0.3	100 mv	0.5	2.0
0.1	200 mv	0.75	1.0

TABLE 5. Resolution and Response time of Inlet/Outlet Transducer, $\mathbf{Xducer}_{I/O}$, for 0.9% Normal Saline Flowing at 350 ml/min

Calculations of amount of fluid passing through the *transducer*, $\mathbf{Xducer}_{I/O}$, @ Flow Rate = 350 ml/min:

A flow rate of 350 ml/min is equivalent to:

5.8 ml per 1 sec
11.6 ml per 2 secs
29.2 ml per 5 secs
58.3 ml per 10 secs

The volume of fluid passing through the 1 inch of IV tubing of 3/32" I.D. within $\mathbf{Xducer}_{I/O}$ is as follows:

$\mathbf{V_1}$ = Volume of Fluid in 1" of 3/32" I.D. tubing

$= \pi \times \text{radius}^2 \times \text{length}$

$= \pi \times .047^2 \times 1 \times 2.54^3 \text{ cm}^3 / 1 \text{ in}^3$

$= 0.114 \text{ cm}^3$ (or $\approx$ 0.114 ml)

4.3.2 Internal Temperature Monitoring

Characterization of the Temperature Monitoring Transducer(**Xducer**$_{Internal}$) for monitoring temperature internal to the heating cavity was performed for the configuration shown in **Figure 5** where a waveguide detection antenna(WR187) is placed within the side wall of the heating cavity.

The design of this transducer has been previously discussed in **Section 3.3.3.** It is used to measure the temperature of the fluid flowing through the IV tubing around the bobbin inside the heating cavity. This is necessary to assure that temperatures inside the heating cavity are known at all times in the event that fluid flow stops and rapid heating occurs in the fluid trapped inside the heating cavity.

The experimental protocol used was to observe the temperature change detected by the radiometer as the temperature of the fluid inside the heating cavity gradually changed by approximatly 10°C. Since the aperture of the waveguide element covers the length of the bobbin of IV tubing along its vertical axis, the fluid temperature changes along the axis from top to bottom as fluid at a new temperature is introduced to the inlet port at the top of the bobbin. A slow flow rate of 50 ml/min was chosen so that the change in radiometer output could easily be seen as the fluid at a new temperature progressed through the IV tubing on the bobbin. The experimental setup for measuring the Temperature Sensitivity of the waveguide mounted inside the heating cavity is as follows:

1. IV tubing threaded along bobbin inside heating cavity. Approximate lenth of bobbin is 2 inches. The length of IV tubing wrapped around bobbin is approximately 78".
2. Prior to the Input of **Xducer**$_{Internal}$, the IV tubing is split by a "Y" junction. One branch of the "Y" placed in a reservoir of Saline at a temperature of **T1** ≈ 34°C and the second branch placed in a reservoir of Saline at a temperature of **T2** ≈ 24°C.
3. The temperature of Fluid flowing into **Xducer**$_{Internal}$ was switched between **T1** and **T2** by clamping and opening the appropriate branch of the "Y" junction.
4. Temperature changes, **ΔT**, of approximately 10°C were achived using this mechanism.

Results of experimental trials are shown in **Figure 15.** The flow rate used in these trials was 50 ml/min ±10 ml/min. This flow rate is equivalent to:

0.8 ml per 1 sec
4.2 ml per 5 secs
8.3 ml per 10 secs

From the calculations presented with **Table 5,** it was shown that there are approximately 0.114 ml per inch of IV tubing (3/32" I.D.). Therefore for the 78" length of tubing wound on the bobbin and used in this experiment, there are approximately 10 ml (= 0.114 ml x 78") of fluid . The data presented in **Figure 15,** shows that change in fluid temperature detected by the waveguide antenna mounted along the vertical axis of the bobbin matches almost exactly the excursion of the cooler liquid through the bobbin. A temperature change of 50% of the maximum temperature change is shown at approximately 5 seconds. By the above calculations, we can see that at 5 seconds the volume of fluid at the new, cooler, temperature in the bobbin is

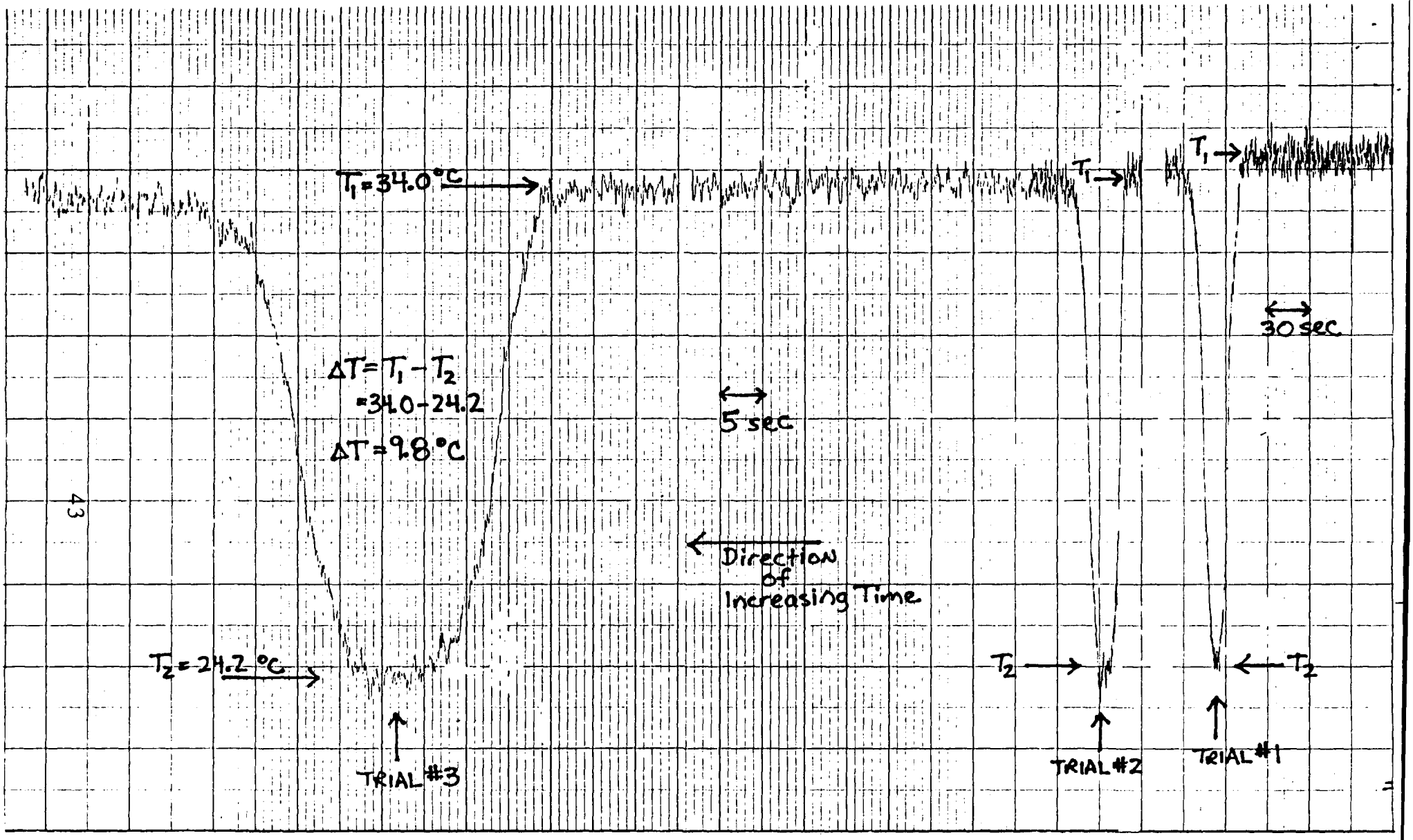


FIGURE 15 **Temperature Measurement Inside the Heating Cavity Using Xducer$_{Internal}$.**

PROCEDURE:
1. Waveguide antenna positioned into one side of the heating cavity.
2. Switch Fluid Input between two reservoirs: Reservoir#1 @ T1≈34°C, Reservoir#2 @ T2≈24°C.
3. Avg fluid temperature measured along length(≈78") of IV tubing wound on bobbin inside heating cavity

approximately 4.2 ml or 50% of the volume. 100% of the maximum temperature change is observed after approximately 10 seconds when about 8.3 ml of fluid has flowed through the bobbin; this corresponds to the calculated volume of fluid of about 9 ml. The data is summarized in **Table 6.**

Trial#	Flow Rate ml/min	T1 °C	T2 °C	ΔT °C	Integration Time Constant τ (secs)	Response Time for 50% of Change secs	Response Time for 100% of Change secs	*Chart Speed*
1	50	34.6	25.0	9.4	0.1	5	10	1div/30ecs
2	50	34.3	24.2	10.1	0.1	5	10	1div/30secs
3	50	34.0	24.2	9.8	0.1	5	10	1div/ 5secs

Table 6. Response Time fo₁ Temperature Changes along the IV Bobbin (Detected by the transducer, $Xducer_{Internal}$, mounted within sidewall of the Heating Cavity)

In conclusion, these data for temperature measurement within the cavity show that the waveguide antenna placed inside the heating cavity and along the vertical axis of the bobbin does indeed give an **Integrated** or **Averaged** value of the fluid in the bobbin itself.

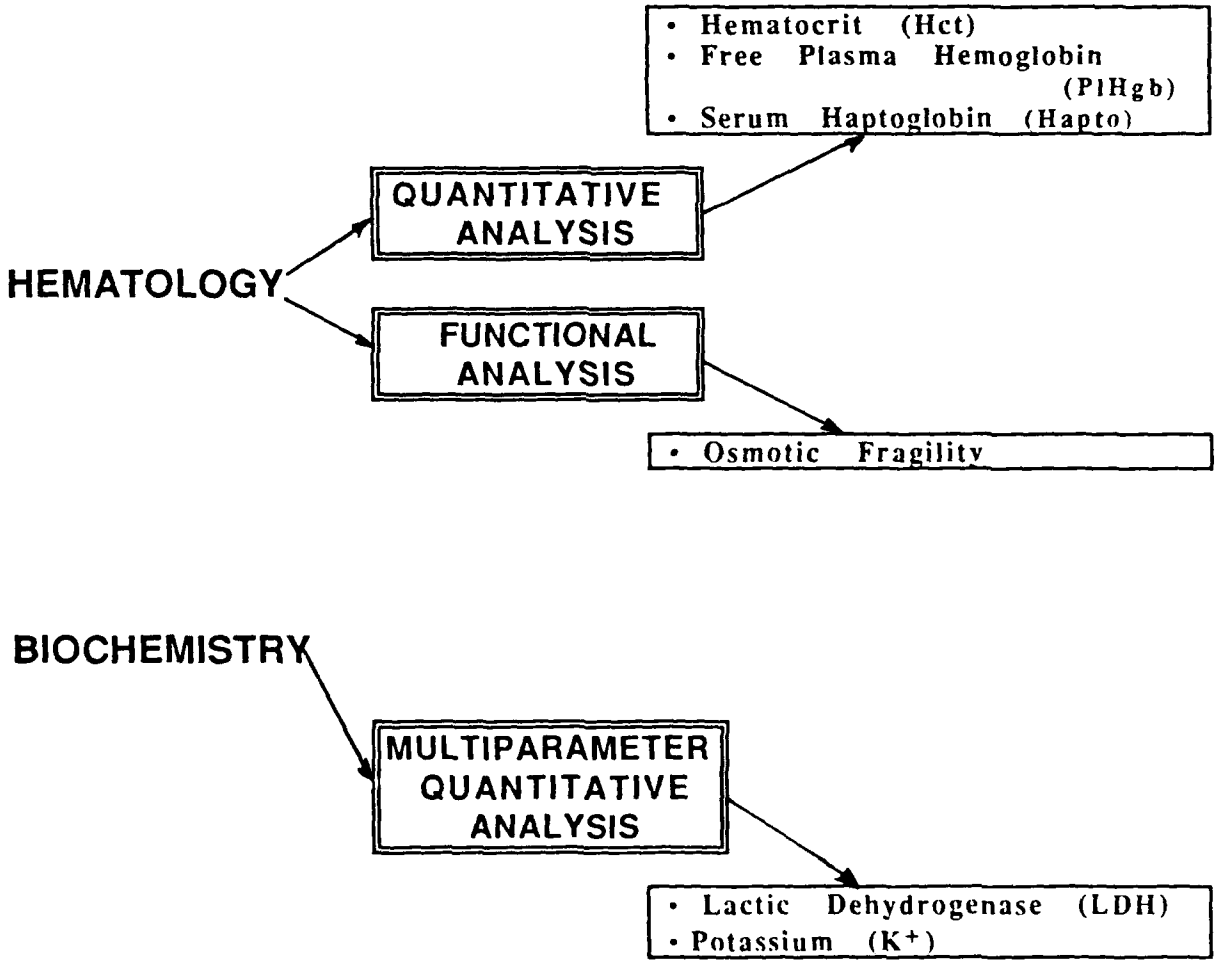
The response rates shown in **Table 6** are slow(10 seconds) but that is because it took 10 seconds for the warm fluid to infiltrate the entire length of tubing on the bobbin at a flow rate of 50 ml/min. Again the slow flow rate of 50 ml/min was chosen so that the change in radiometer output could easily be seen as the fluid at a new temperature progressed through the IV tubing on the bobbin When the fluid temperature along the bobbin increases rapidly due to increased heating power or higher flow rates, the resulting response time would decrease. It is resonable to expect that the response time would be similar to that of the $Xducer_{I/O}$ used on the input/output ports which has been shown to be less than 1 second with a resolution of 0.75°C (see **Table 5**).

4.4 Biologic Analysis

Experimental trials for evaluating the performance of the microwave blood warmer, by examining the constituency of IV fluids and blood heated by the system, were conducted using the test circuit shown in **Figure 2.** The protocols used for these tests are described in **Section 3.5.** All tests were conducted by the Department of Surgery Staff at New England Medical Center in their facilities in Boston, MA.

For IV Fluids, trials to determine changes in plasticizer levels of microwave heated samples were conducted.

For Blood Samples, standard clinical laboratory tests were performed. Of the many biologic assays, those parameters chosen for statistical analysis to best show any constituency changes between the control samples and the microwave heated samples are illustrated by the following diagram:



4.4.1 IV Fluid: Plasticizer Analysis

Following the protocol described in **Section 3.5.1**, trials were conducted to measure the fluid level of the plasticizer Di-Ethyl Phthalate(DEHP) in two commonly used IV Fluids after heating samples with the in-line microwave warmer. DEHP is used in common PVC IV tubing. Tests to analyze the level of DEHP were done at the laboratory of Mae Jacobson, MD at the Blood Bank of the Children's Hospital of Boston, MA. Using chromatographic techniques, the trace levels of DEHP found in the microwave heated samples did not change from the levels found in the control samples.

In the blood, levels greater than 7 mg/Deciliter in blood stored for 21 days are considered toxic. The trace amounts detected by our tests are well below this level.

4.4.2 Blood Hematology

Following the protocol described in **Section 3.5.2**, trials were conducted to measure the consituency differences between blood samples heated with the in-line microwave warmer and control blood samples drawn from volunteers. The approximate flow rates at which the samples were infused through the test circuit(using the Cordis Syringe Pump), and the resultant temperature elevation measured between the inlet and outlet ports of the heating cavity, are listed in **Table 7**. A flow rate of 300 ml/min to 350 ml/min was used in most of the trials. At this flow rate the blood was heated approximately 20°C. Other flow rates were evaluated, as well. At 550 ml/min the blood was heated approximately 10°C; and at 250 ml/min the temperature rise was approximately 25°C. These temperature elevations of 10°C to 25°C would be typical levels required for warming room temperature or refrigerated blood/IV fluids.

Laboratory results from the analysis of the blood samples for Trial#2 through *Trial#10 are listed in* **Table 8** *for those parameters selected* to be most appropriate for detecting changes in constituency due to heat. Determination of statistically significant changes to these parameters were analyzed using the Student's T test. A summary of the statitistical analysis is given in **Table 9** for two groups of data:

Group I: This grouping was for comparing the constituency difference between the blood samples heated once*(one-pass through the test circuit)* and the control samples.

Group II: This grouping was for comparing the constituency difference between all the heated blood samples*(one-pass , two-pass and three-pass heating through the test circuit)* and the control samples.

For the hematology analysis complete blood counts were performed. Statistical analysis of the changes in hematocrit showed no significant differences for Group I or Group II. Hemoglobin, leukocytes and red cell volume data were examined and found to be without change.

Further hematologic analysis for hemolysis was measured by free plasma hemoglobin(PlHgb) levels, which are expected to rise with hemolysis, and serum haptoglobin(hapto) levels which will fall in hemolysis. Osmotic fragility was determined in half of the trials for samples that were heated three times, so that any effect would be maximized. The continuous flow method, which dilutes the blood sample in saline, was used to determine osmotic fragility. Changes in optical density of the solution were measured, and the % hemolysis versus the % NaCl was plotted as shown in **Figure 16.** Results were all within the normal limits of the New England Medical Center laboratory normal limits denoted by "S-shaped curve" on the graphs.

TRIAL #	FLOW RATE (approximate) (ml/min)	T in (°C)	T out (°C)	ΔT (°C)
1a	0	PRACTICE TRIAL		
1b	350			
1c	350			
1d	350			
2a	0	17.0	17.0	0.0
2b	350	17.6	35.1	17.5
2c	350	22.3	39.5	17.2
2d	350	20.7	37.0	16.3
3a	0	15.0	15.0	0.0
3b	300	18.0	37.6	19.6
3c	300	17.6	37.6	20.0
3d	300	17.9	38.9	21.0
4a	0	17.0	17.0	0.0
4b	300	20.1	40.1	20.0
4c	300	16.0	36.6	20.6
4d	300	17.6	37.5	19.9
5a	0	15.5	15.5	0.0
5b	350	18.1	35.7	17.6
5c	350	20.9	36.1	15.2
5d	350	20.3	37.4	17.1
6a	0	16.0	16.0	0.0
6b	300	19.2	37.4	18.2
6c	300	19.3	38.9	19.6
6d	300	17.7	36.8	19.1
7a	0	18.0	18.0	0.0
7b	550	21.7	30.4	8.7
7c	550	24.3	35.0	10.7
7d	550	24.1	35.2	11.1
8a	0	10.0	10.0	0.0
8b	250	17.0	41.2	24.2
8c	250	16.5	42.4	25.9
8d	250	17.6	43.3	25.7
9a	0	11.0	11.0	0.0
9b	300	17.6	41.9	24.3
9c	300	17.6	38.4	20.8
9d	300	15.8	37.9	22.1
10a	0	15.0	15.0	0.0
10b	300	16.2	39.2	23.0
10c	300	15.9	36.6	20.7
10d	300	16.4	37.0	20.6

TABLE 7. DATA RECORDED FOR BLOOD WARMING TRIALS
Temperatures Measured with Luxtron Fluoroptic Thermometry System
Samples Pumped through System with Cordis Injector Syringe Pump

PARAMETER	Units	CONTROL TRIAL 2A	3A	4A	5A	6A	7A	8A	9A	10A	AVG	VAR	SD
PlHgb	mg/DL	31	28	22	17	7	5	22	29	13	19.3	80.2	9.0
Hapto	mg/DL	31	30	81	64	82	156	98	88	132	84.7	1537.1	39.2
K+	meq/L	3.5	3.7	3.3	3.7	3.6	3.6	3.7	3.5	3.9	3.6	0.03	0.16
LDH	IU/L	144	100	134	123	117	107	107	104	113	116.6	191.8	13.8
Hct	%	38	48	45	45	42	35	43	42	43	42.3	13.3	3.7

PARAMETER	Units	ONE-PASS HEATING TRIAL 2B	3B	4B	5B	6B	7B	8B	9B	10B	AVG	VAR	SD
PlHgb	mg/DL	22	27	19	8	5	8	23	22	21	17.2	56.8	7.5
Hapto	mg/DL	34	30	82	64	82	97	158	87	135	85.4	1562.2	39.5
K+	meq/L	3.5	3.7	3.2	3.6	3.6	3.7	3.5	3.5	3.9	3.6	0.03	0.2
LDH	IU/L	141	106	140	128	124	126	119	116	134	126.0	115.8	10.8
Hct	%	38	48	45	45	43	35	42	44	43	42.6	13.6	3.7

PARAMETER	Units	TWO-PASS HEATING TRIAL 2C	3C	4C	5C	6C	7C	8C	9C	10C	AVG	VAR	SD
PlHgb	mg/DL	23	32	24	8	6	6	26	17	24	18.4	82.7	9.1
Hapto	mg/DL	38	30	77	63	83	96	152	90	132	84.6	1403.1	37.5
K+	meq/L	3.5	3.8	3.3	3.6	3.6	3.8	3.8	3.5	3.9	3.6	0.03	0.18
LDH	IU/L	134	107	145	136	122	122	135	116	119	126.2	127.5	11.3
Hct	%	38	47	45	46	44	36	42	43	43	42.7	11.6	3.4

PARAMETER	Units	THREE-PASS HEATING TRIAL 2D	3D	4D	5D	6D	7D	8D	9D	10D	AVG	VAR	SD
PlHgb	mg/DL	19	29	26	7	10	10	31	12	24	18.7	74.7	8.6
Hapto	mg/DL	39	30	75	64	75	93	148	88	129	82.3	1299.6	36.0
K+	meq/L	3.6	3.9	3.5	3.6	3.6	3.6	3.9	3.6	3.9	3.7	0.02	0.15
LDH	IU/L	134	107	161	145	138	142	133	126	128	134.9	194.8	14.0
Hct	%	38	47	44	43	42	35	42	40	42	41.4	10.7	3.3

TABLE 8. LIST OF SELECTED BLOOD ASSAY DATA FOR ALL TRIALS

TRIALS B + C + D		
AVG	VAR	SD
18.1	66.3	8.1
84.1	1313.9	36.2
3.6	0.03	0.17
129.0	150.6	12.3
42.2	11.3	3.4

STUDENT T Test (T ratios)	
Trial B df=16	Trials B + C + D df=34
0.54	0.36
0.04	0.04
0.41	0.41
1.62	2.41
0.13	0.08

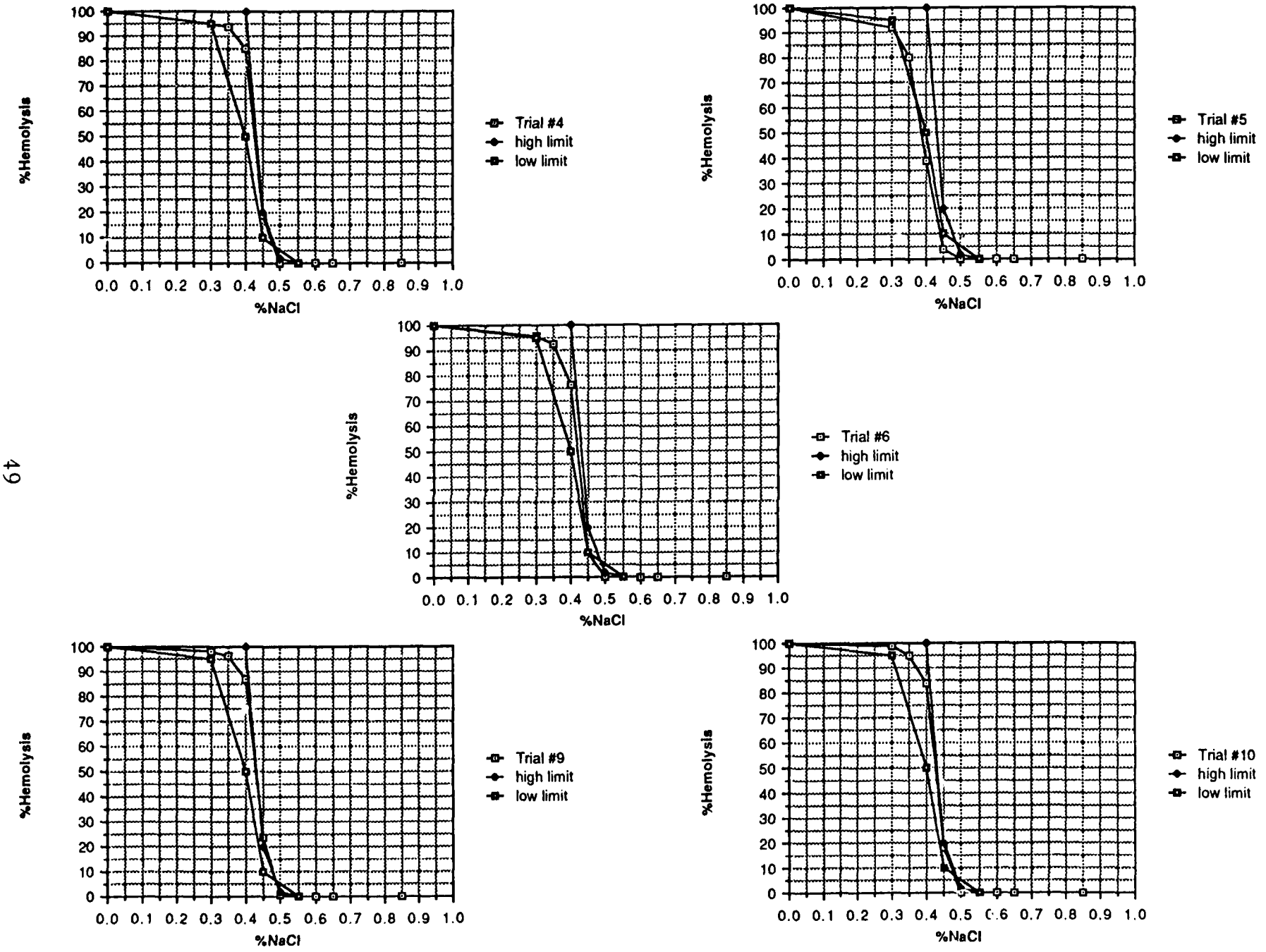


FIGURE 16. Osmotic Fragility Results for Human Volunteer Blood Trial #4,5,6,9,10.

PARAMETER	CONTROL		GROUP I			GROUP II		
	Avg	±s.d.	Avg	±s.d.	T test (Df=16)	Avg	±s.d.	T test (Df=34)
PlHgb	19.3	±9.0	17.2	±7.5	0.54(N.S.)	18.1	±8.1	0.36(N.S.)
Hapto	84.7	±39.2	85.4	±39.5	0.04(N.S.)	84.1	±36.2	0.04(N.S.)
K+	3.6	±0.2	3.6	±0.2	0.41(N.S.)	3.6	±0.17	0.41(N.S.)
LDH	116.6	±13.8	126.0	±10.8	1.62(N.S.)	129.0	±12.3	2.41(p<.05)
Hct	42.3	±3.7	42.6	±3.7	0.13(N.S.)	42.2	±3.4	0.08(N.S.)

TABLE 9. Averages & Statistical Analysis(Student's T test) of Blood Constituency

4.4.3 Blood Biochemistry

Lactic acid dehydrogenase(LDH) levels, listed in **Tables 8** and **9**, were selected as the most relevant serum enzyme marker of hemolysis. For one pass heated samples(Group I) no statistically significant changes from the control levels were found as shown in **Table 9**. Only a slight rise in LDH was detected for the samples heated two and three times(Group II). Although there was a statistically significant difference detected here, the absolute value of LDH level for these samples are within normal limits for this enzyme. Other enzymes, such as creatine phosphokinase and alkaline phosphase as well as total serum protein/albumin, were also studied and showed no differences with heating.

Electrolytes were evaluated and potassium data of heated samples showed no statistically significant changes from control levels as reported in **Tables 8** and **9.** Other electrolytes and urea nitrogen were also examined and showed no changes.

Note: To establish the validity of the laboratory analysis of the blood samples, a test sample was overheated to an average temperature of 80°C by the in-line microwave blood warmer to assure hemolysis. The laboratory analysis of the parameters selected here to indicate hemolysis, did indeed show large differences to amounts considered normal by the testing laboratory. These results are listed below in Table 10:

PARAMETER	UNITS	CONTROL SAMPLE (unheated)	HEATED SAMPLE (heated to 80°C)	LABORATORY NORMAL VALUE
PlHgb	mg/DL	22	225 *(severe hemolysis)*	< 10
Hapto	mg/DL	98	<5 *(severe hemolysis)*	50 to 200
K+	meq/L	3.7	> 10	3.5 to 5.0
LDH	Iu/L	107	> 2000	to 170
Hct	%	43	46	35 to 45

TABLE 10. Verification of hemolysis detection in overheated blood

5.0 DISCUSSION

The Phase I feasibility study has demonstrated operation of an in-line microwave warming device capable of heating blood and IV fluids rapidly and uniformly. The temperature monitoring capabilities of the microwave radiometer and associated transducers provide the necessary mechanism for feedback control of the energy source.

The small size of the heating cavity and the potential for packaging the IV tubing insert as a sterile and disposable element make the system readily configurable as a portable unit for field use during administration of blood or IV fluids.

In this study the heating of whole blood with rapid flows and large temperature elevations resulted in minimal if any perturbations in blood parameters. The advantage of using whole blood heating for feasibility studies lies in well established control parameters. Heating of blood bank blood is envisioned for future tests.

Some of the small changes in blood constituency detected in this study can be attributed to factors other than the effects of heating. The elevation of free plasma hemoglobin in the control samples are perhaps due to the blood drawing technique or to the trauma induced by the injection system. Exposure to microwave heating caused no further elevation of this parameter. No other parameters analyzed by the laboratory were found to be abnormal in either the control or heated blood. Although aggregate LDH data on heated blood showed a significant difference, the total value of LDH rise was well within the normal values for this enzyme.

The design of the microwave warming device is now ready to proceed to Phase II development. Results from the microwave characterization tests and *in-vitro* heating experiments in this Phase I study have established that the efficiency and efficacy of the device are excellent for the application of in-line warming of blood and IV Fluids.

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APPENDIX

Human Investigation Review Committee

Approvals

New England
Medical Center Hospitals

1796 Boston Dispensary
1894 Floating Hospital for Infants and Children
1938 Pratt Clinic
1948 New England Center Hospital
1958 Rehabilitation Institute

Tufts University

1893 School of Medicine
1899 School of Dental Medicine
1979 School of Veterinary Medicine
1980 Sackler School of Graduate Biomedical Sciences

Human Investigation Review Committee
(617) 956-5363

David Greenblatt, M.D.
Chairman

Judy A. Tesnow
Administrator

NOTICE OF PROTOCOL APPROVAL

Principal Investigator: CLEVELAND, RICHARD M.D.
H-SUR-
Box 203
NEMCH

Login No.: 1087

Protocol Title:

MICROWAVE BLOOD WARMING

Protocol Approved: Date of Approval: 06/16/87

- as submitted _X_

- contingent upon conditions described on Page 2 ____

Consent Form:

- approved as submitted, dated copy enclosed _X_

- must be revised per enclosed sample and returned to HIRC Office for approval before the Study may begin ____

Copy of Human Protection Form as sent to Funding Agency: - enclosed ____ - not required _X_

Regulations regarding Clinical Research:

1. the approval is valid for one (1) year from the date of approval (unless otherwise stipulated by HIRC).

2. all unanticipated adverse reactions/side effects encountered in this study must be promptly reported to HIRC.

3. any changes or modifications in the study protocol or consent form must be reviewed and approved by HIRC prior to implementation.

4. only the HIRC approved and dated consent form must be utilized. Please discard all prior versions.

THIS NOTICE OF APPROVAL MUST BE RETAINED WITH YOUR RESEARCH FILES.

July 1, 1987
Date

D Greenblatt
Signature of Chairman/Vice Chairman/Administrator
Human Investigation Review Committee

Consent Form

The Committee approved the enrollment of adult normal volunteers, 19-50 years of age, in this blood drawing study.

The Committee waived the requirement of written consent and approved the use of a consent statement which should be given to the volunteer and verbal consent obtained.

Enclosed for your use is a copy of the approved consent statement which has been dated with the approval date.

NEW ENGLAND MEDICAL CENTER

CONSENT FORM

MICROWAVE BLOOD WARMING STUDY

DRS. CLEVELAND/CONNOLLY/HARRIS/SCHWAITZBERG

PURPOSE: The purpose of these studies is to determine the safety and efficacy of a device for warming blood to body temperature or above without damaging that blood. An ability to do this will greatly improve our ability to treat patients with low body temperature due to injury, surgery, exposure, or other causes.

As a volunteer in this research study, you will be asked to give **one** sample of blood (no more than 100cc - approximately 1/2 cup) one time. Dr. Schwaitzberg or a person assisting him and trained in venipuncture will draw the sample. In return you will receive payment of $0.50 per cc of blood with a minimum of $20.00 for a needle puncture.

There may be slight discomfort to your arm when the needle is inserted into a vein and a small bruise may develop.

Your participation will result in no direct benefit to you but may provide generally useful knowledge.

You are free not to participate or to withdraw at any time, and your withdrawal will not effect your future care or treatment at this institution.

Your medical records and identity will not be disclosed except as required by law.

You are free to ask questions concerning this study at any time.

You may contact Dr. Connolly, X5613 or Dr. Schwaitzberg, X7017 at any time if you have questions or problems about this study.

Approved 6/16/87
Valid through 6/16/88